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13. ABSTRACT *(Maximum 200 words)*
Each year an estimated one million women elect to have surgical sterilization. This is performed by a laparoscopic procedure which can be severe enough to warrant an unplanned admission. With an increased understanding of the physiological basis of pain, classes of drugs not normally associated with pain reduction are now being investigated based on their ability to interact with receptors in the pain pathway. Experimental studies have shown that the N-methyl-D-aspartate (NMDA) receptor plays a significant role in neuronal "wind-up", a state of hyperalgesia that can last from hours to days following injury or trauma.. Interfering with the NMDA receptor prior to surgical stimuli, wind-up is prevented resulting in decreased pain and analgesic requirements following surgery. Dextromethorphan, a readily available nonopioid antitussive in clinical use for more than 40 years, is one such NMDA receptor Anticosti. This prospective, randomized, double blind pilot study compared the effects over time when patients received dextromethorphan versus placebo-emptively. The sample was comprised of 14 subjects undergoing laparoscopic tubal ligation under general endotracheal anesthesia at regional military medical center for the Pacific Basin. Patients were ASA physical category I or II and at least 18 years of age and assigned to one of two groups. Group I received 60 mg of dextromethorphan orally, and Group II received an oral placebo. Postoperative pain was assessed using an 11 point Numeric Rating Scale (NRS) at eight time intervals. Additionally, a follow-up questionnaire and 48-hour postoperative telephone call were used to collect data on the patients' satisfaction of being in the study. The Student's t-test was used to determine homogeneity between the two groups. Following analysis, a statistically significant difference was found in two areas. Patients who received dextromethorphan 60 mg orally before surgery had a significant decrease in postoperative pain ($p < 0.04$). The amount of Roxicet required postoperative was statistically less in the dextromethorphan group ($p < 0.02$). The preoperative use of dextromethorphan may significantly decreased the amount of postoperative pain experienced with a resultant decrease in need for narcotic analgesics.

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THE EFFECT OF PRE-EMPTIVE ADMINISTRATION OF DEXTROMETHORPHAN ON POSTOPERATIVE PAIN IN PATIENTS UNDERGOING INTERVAL LAPAROSCOPIC TUBAL STERILIZATION

By

CPT Brian M. Pitcher, B.S.N.

A Thesis

Submitted in partial fulfillment

of the requirements for the degree of

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ABSTRACT

Each year in the United States, an estimated one million women elect to have surgical sterilization. This is usually performed by a laparoscopic procedure on an outpatient basis despite problems with post-laparoscopic pain, which can be severe enough to warrant an unplanned admission. With an increased understanding of the physiological basis of pain, pain transmission and pain perception, classes of drugs not normally associated with pain reduction are now being investigated based on their ability to interact with receptors in the pain pathway.

Experimental studies have shown that the N-methyl-D-aspartate (NMDA) receptor plays a significant role in neuronal "wind-up", a state of hyperalgesia that can last from hours to days following injury or trauma. By interfering with the NMDA receptor prior to surgical stimuli, wind-up is prevented resulting in decreased pain and analgesic requirements following surgery. Dextromethorphan, a readily available nonopioid antitussive in clinical use for more than 40 years, is one such NMDA receptor antagonist.

This prospective, randomized, double blind pilot study compared the effects over time when patients received dextromethorphan versus placebo pre-emptively. The sample was comprised of 14 subjects undergoing laparoscopic tubal ligation under general endotracheal anesthesia at a regional military medical center for the Pacific Basin. The patients were ASA physical category I or II and at least 18 years of age and assigned to one of two groups.

Group I received 60 mg of dextromethorphan orally, while Group II received an oral placebo. Postoperative pain was assessed using an 11 point Numeric Rating Scale (NRS)at eight time intervals. Additionally, a follow-up questionnaire and 48-hour

postoperative telephone call were used to collect data on the patients' satisfaction of being in the study.

The Student's t-test was used to determine homogeneity between the two groups. Following analysis, a statistically significant difference was found in two areas. First, patients who received dextromethorphan 60 mg orally before surgery had a significant decrease in postoperative pain ($p < 0.04$). Second, the amount of Roxicet® required postoperatively was statistically less in the dextromethorphan group ($p < 0.02$). The preoperative use of dextromethorphan may significantly decrease the amount of postoperative pain experienced with a resultant decrease in need for narcotic analgesics.

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The Committee for the
Protection of Human Subjects

NOTICE OF APPROVAL TO BEGIN RESEARCH December 15, 2000

HSC-SN-00-030 "The Effect of Preemptive Administration of Dextromethorphan on Postoperative Pain in Patients Undergoing Interval Laparoscopic Bilateral Tubal Sterilization"
P.I.: Brian Pitcher, MSN Student

PROVISIONS: Unless otherwise noted, this approval relates to the research to be conducted under the above referenced title and/or to any associated materials considered at this meeting, e.g. study documents, informed consent, etc.

APPROVED: At a Convened Meeting

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CHAIRPERSON: Anne Dougherty, MD 12/19/00

Subject to any provisions noted above, you may now begin this research.

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CHAPTER I

Modern technological advances and heightened consumer knowledge are pushing the health care establishment to simultaneously increase patient satisfaction while making health care more economical. For instance, the number of outpatient procedures has continually increased, while the length of hospital stays has decreased (Poole, 1999). As a consequence, health care providers have emphasized the importance of achieving improved levels of pain control in order to increase patient comfort, expedite recovery, and decrease length of hospital stay. Interval Laparoscopic Bilateral Tubal Sterilization (ILBTS) is a surgical procedure routinely performed on women of childbearing age and is routinely performed as an ambulatory surgery procedure. As with most surgical procedures, ILBTS has a reported degree of pain postoperatively which ranges from pain similar to menstrual cramping to severe enough pain to justify hospital admission (Cade & Kakulas, 1995).

Pain control in the perioperative environment is a critical factor in achieving patient satisfaction and reducing costs. Anesthesia providers, in particular, are increasingly focused on techniques that improve pain control and therefore patient satisfaction. Pre-emptive analgesia is one approach to effective pain control. The concept of pre-emptive analgesia is to block or reduce surgical pain before it begins. After analyzing more than 7,000 published studies, the Agency for Health Care Policy and Research concluded aggressive pain prevention was better than treatment of pain once it was established (Agency for Health Care Policy and Research, 1994). Traditionally, pain has been treated postoperatively by the administration of an analgesic, usually an opioid narcotic. Unfortunately, there are numerous side effects associated with opioid narcotics such as

respiratory depression, constipation, and postoperative nausea and vomiting. These untoward effects can result in unexpected admission to the hospital, defeating the goals of reducing costs and improving patient satisfaction. Research continues into finding new drugs, and new uses for current drugs in the hopes of avoiding some of these side effects.

Dextromethorphan is a drug widely used for its antitussive action. It is being considered in this study, not for this action, but because of its noncompetitive antagonism at the N-methyl-D-aspartate (NMDA) receptor (Hardman, Limbard, Molinoff, Ruddon, & Gilman, 1996). The NMDA receptor is one of the Principal receptors in the CNS associated with excitatory neurotransmission. During "normal" pain transmission when the threshold for the NMDA receptor has not been met, the NMDA receptor is inactive. When a painful stimulus is either sustained or intense enough to reach a critical level, the receptor is activated resulting in depolarization of the neuron. This mechanism is thought to be responsible for lowering the firing threshold leading to central hypersensitivity ("wind-up"), an enhanced response to painful stimuli (Henderson, Withington, Wilson, & Morrison, 1999). Furthermore, dextromethorphan has no sedative or respiratory depressant effects unlike narcotics or other NMDA antagonists (e.g. ketamine, magnesium sulfate).

Statement of the Problem

Previous studies involving dextromethorphan's use as an analgesic adjunct have produced inconclusive results. Some studies have concluded that dextromethorphan decreases postoperative pain with a concomitant reduction in analgesic use (Chia, Liu, Chow, & Lee, 1999; Henderson, et al., 1999; Kawamata, Omote, Kawamata, & Namiki, 1998). Other studies have failed to show any effect on pain levels or amount of analgesics

required (Grace et al., 1998; Rose, Cuy, Cohen, & Schreiner, 1999). The goal of this research project is to determine if the administration of oral dextromethorphan has an effect on postoperative pain following bilateral tubal ligation.

Conceptual Framework

The series of events involved in the transmission of pain is as follows: with the advent of acute pain, nociceptive impulses are transmitted via peripheral fibers to the dorsal horn in the spinal cord; this involves transmission via both myelinated A-δ, and unmyelinated C-fibers. The A-δ fibers faithfully transmit painful stimuli that are proportionate to the duration and intensity of the pain. The Principal excitatory neurotransmitter in the central nervous system is glutamate, which when released from presynaptic C-fiber nerve terminals diffuses across the synaptic cleft where it is free to act on NMDA receptors. If the stimulus is of sufficient duration and/or intensity, NMDA receptors located on neurons in the dorsal horn of the spinal cord are activated (Appendix A).

In their inactive state, the NMDA receptors are bound with magnesium. Glutamate's action on the NMDA receptor causes magnesium to be released from the ion channel. This release allows for an influx of calcium and sodium ions through the receptor channel. When the NMDA receptor is activated, the result is neuronal depolarization and increased neuronal excitability. Build up of an enhanced painful stimulus produces a process known as "wind up" where the threshold for triggering an action potential is lowered. This causes an earlier and more intense discharge when threshold is achieved (Henderson et al., 1999). Intensified potentiation of pain transmission can last from hours to days.

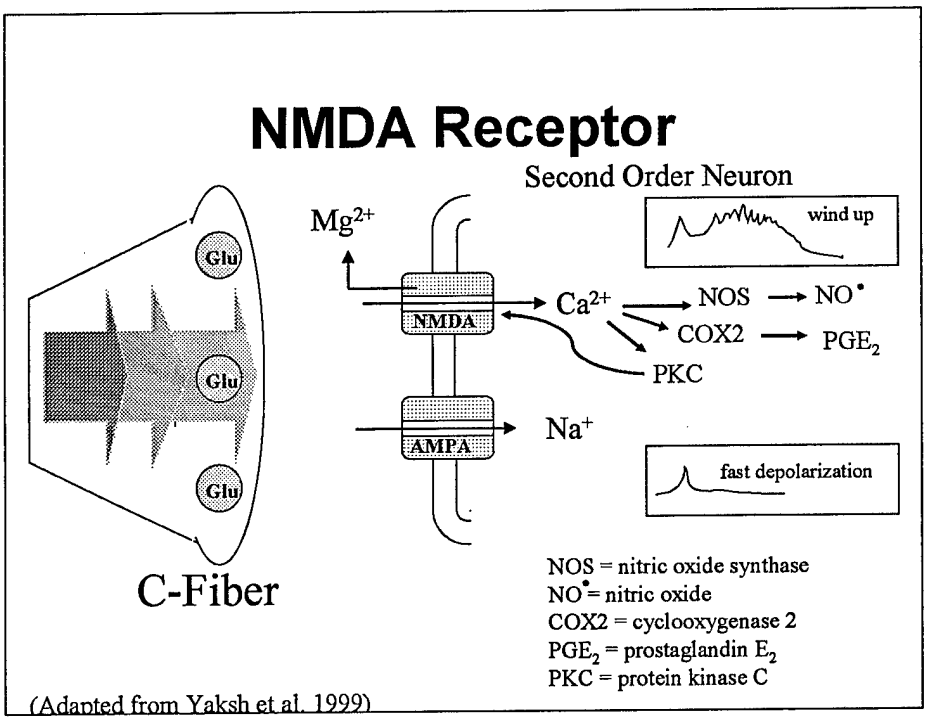

Figure 1. NMDA Receptor Model for Pain

Dextromethorphan should interrupt the formation of central hypersensitization by noncompetitive antagonism of the NMDA receptor. Inhibition of calcium influx at the NMDA receptor results in decreased neuronal excitability. This is the theoretical basis of the antinociceptive properties seen by dextromethorphan in previous studies (Chia et al., 1999; Henderson et al., 1999). Thus, it is theorized that blocking hypersensitization via the NMDA receptor prevents the enhanced response to painful stimuli.

Purpose

The purpose of this research is to determine the effectiveness of dextromethorphan as a pre-emptive intervention for postoperative pain relief. This study will compare the pain relief qualities and analgesic-sparing capabilities of dextromethorphan with a placebo in women undergoing ILBTS.

Definitions of Terms

Interval Laparoscopic Bilateral Tubal Sterilization (ILBTS)

Conceptual. A surgical procedure (in women who are at least six weeks postpartum) that blocks the movement of the egg from the ovaries to the uterus resulting in the inability to become pregnant. (Pelland, 1977)

Operational. The lower abdomen is entered laparoscopically and the fallopian tubes are occluded either by cauterization, application of Fallope rings or Filshie clips.

Pre-emptive Analgesia

Conceptual. The administration of medication prior to a surgical procedure or induction of anesthesia, in an attempt to attenuate postoperative pain.

Operational. 60 mg of dextromethorphan given orally 30-60 minutes prior to induction of anesthesia.

Postoperative Pain

Conceptual. An unpleasant sensory and emotional experience associated with actual or potential tissue damage, caused by stimulation of specialized nerve endings following a surgical procedure.

Operational. Any discomfort expressed by the patient postoperatively, as quantified by a verbally administered eleven-point (0-10) numeric rating scale (NRS).

Research Question

Does dextromethorphan reduce acute postoperative pain and analgesic requirements associated with laparoscopic tubal ligation?

Significance of the Problem

Successful inhibition of the NMDA receptor prevents central hypersensitization, or "wind up" from occurring (Kawamata et al., 1998). Clinically, this should result in a decreased level of pain experienced by the patients. A decreased level of pain may result in decreased length of stay, decreased postoperative complications, and decreased admission rates. Furthermore, patients who experience decreased untoward psychological effects associated with pain may have increased positive patient outcomes, and an overall increased patient satisfaction. Decreased pain levels may result in a decreased need for analgesics; thereby, decreasing the risk and severity of analgesic side effects.

Assumptions

1. The patient undergoing ILBTS has postoperative pain.
2. Postoperative ILBTS patients will have similar type pain.
3. Postoperative pain is an undesirable outcome in patients having ILBTS.
4. The pain rating derived from the NRS is an accurate reflection of the level of pain as perceived by the patient.
5. American Society of Anesthesiologist (ASA) physical classifications appropriately identify the patient's health status.
6. Pain is subjective and can be measured most appropriately by the patient.

Limitations

1. Results of this study may be generalized only to patients of ASA physical classification I and II, undergoing laparoscopic bilateral tubal sterilization with general anesthesia.

2. This study was conducted in a military, teaching, medical center that may limit generalizability.
3. Anesthesia care providers possessing various degrees of preparatory education and clinical experience will provide general anesthesia; therefore, anesthesia care between providers will have some variation.
4. Because participants in this study know they are part of a study, the Hawthorne effect will be a consideration in this study. Patients may act differently then they otherwise would due to the knowledge they are participants in the study.

Summary

Patients undergoing ILBTS with unmanageable postoperative pain are subject to a host of untoward psychological and physiological side effects. In addition to unsatisfactory patient care outcomes, unplanned hospital admissions resulting from postoperative pain create an economic burden for a system that is striving for cost containment of health care. The proposed clinical trial will evaluate postoperative pain in patients treated pre-emptively with dextromethorphan. The theoretical reasoning for using dextromethorphan in this manner is that it blocks depolarization of the postsynaptic neuron by binding to the NMDA receptor preventing the movement of calcium ions into the postsynaptic neuron. Therefore, the enhanced central hypersensitive response, "wind-up," is prevented, facilitating a quicker recovery and shorter hospital stay for the patient.

CHAPTER II

Review of Related Literature

Receptors in the Central Nervous System

The need for patient satisfaction, minimal pain and discomfort following surgery are desirable outcomes toward which every anesthesia provider should strive (Henderson et al., 1999). Surgical advances are enabling more procedures to be done on an outpatient basis resulting in patients returning home a few hours after surgery. In the hopes of reducing postoperative pain and analgesic requirements, many investigators are looking at the effectiveness of giving medications pre-emptively to achieve these goals.

With an increased understanding of the physiological basis of pain, pain transmission and pain perception, classes of drugs not normally associated with pain reduction are now being investigated based on their ability to interact with receptors in the pain pathway. One such drug is the NMDA receptor antagonist dextromethorphan, a readily available nonopioid antitussive in clinical use for more than 40 years.

Pain Mechanism of Action

Pain has been described as a subjective feeling of distress, suffering, or agony caused by stimulation of specialized nerve endings. Pain is subjective and cannot be measured externally to the patient. Current pain assessment tools rely on patients to report that they are in pain.

Surgical trauma and the inflammatory process activate the release of substances that cause a sensitization of nociceptors. Peripheral tissue injury results in modification of nociceptive processing at both the peripheral and central nervous systems. Peripheral mechanisms of pain modulation involve the release of bradykinin, a chemical produced

by proteolytic enzymes and released in response to cellular damage. Bradykinin acts as a powerful pain mediating peptide that acts directly on A-δ and C-polymodal receptors (Garrett & McShane, 1999). Bradykinin is also responsible for the activation of the phospholipase A_2 that acts to release arachidonic acid from cell membrane phospholipids. With tissue inflammation, the arachidonic acid is rapidly converted by cyclooxygenase 2 (COX-2) to prostaglandins E_2 and I_2. Both have been associated with primary hyperalgesia.

Pain receptors located in the periphery conduct noxious stimuli by way of A-δ and C-fibers into the dorsal root ganglion continuing into the dorsal horn of the spinal column. Further transmission from this point relies upon chemical mediators crossing a synaptic cleft in sufficient quantities to cause a depolarization on the postsynaptic neuron. This discharge is responsible for the further conduction of the stimuli to the thalamus. From the thalamus, the signal then travels to the postcentral gyrus of the cerebral cortex where the stimulus is interpreted as pain (Berne & Levy, 1995).

Central nervous system modulation of pain involves the neurotransmitter glutamate at the synapse between the first and second order neuron located in the dorsal horn of the spinal cord, predominately in Rexed lamina II. Glutamate acts on the both the α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA) and NMDA receptors. Under normal circumstances painful stimuli cause activation of the AMPA receptor that faithfully transmits the painful stimuli to the thalamus, which then directs the input to the cerebral cortex. Stimuli of low frequency and intensity cause activation of AMPA receptors on the postsynaptic membrane of the second order neuron causing membrane depolarization and propagation of the impulse. The duration and intensity of transmission

are the same as the stimulus. At higher frequency, or intensity, NMDA receptors are activated setting in motion a cascade of intracellular events leading to the phenomenon referred to as "wind-up" or "long term potentiation" (LTP) (Hardman et al., 1996), (Figure 1). Wind-up causes an exaggerated response to incoming stimuli resulting in increased amplitude and duration of neuron firing that is perceived as hyperalgesia (Rose et al., 1999). This wind-up, or sensitization of second-order neurons in the dorsal horn of the spinal cord, results in a continued volley of afferent pain impulses to the brain, even after the peripheral stimulus has ceased. Hyperalgesia is a state that can last for hours or days.

Recently researchers have theorized that blockade or inhibition of the NMDA receptor prior to the arrival of a noxious stimulus should be able to prevent or reduce the degree of "wind-up" that the patient would experience (Urban & Gebhart, 1999; Woolf & Thompson, 1991; Yaksh, Hua, Kalcheva, Naoki-Taguchi, & Marsala, 1999). This should result in a decrease in the intensity and duration of pain experience and subsequent decrease in the need for analgesic usage, (Appendix A, Figure 4).

To date, clinical evaluation of NMDA antagonists in acute pain have involved three compounds: magnesium, ketamine, and dextromethorphan (Henderson et al., 1999). Those examining the use of magnesium have not shown any benefit (Liu, Hollmann, Liu, Hoenemann, & Durieux, 2001; Wilder-Smith, Knopfli, & Wilder-Smith, 1997), unlike those studying ketamine (Royblat et al., 1993; Tverskoy, Korotkoruchko, & Katz, 1994). While ketamine has been shown to decrease acute postoperative pain, its side effect profile, including hallucinations and delirium, makes it a poor choice for pain reduction (Henderson et al., 1999). Dextromethorphan, a noncompetitive NMDA receptor

antagonist, binds to a specific site on the receptor preventing activation of the receptor. Without this activation the sequence of intracellular events leading the hyperalgesic state are prevented from occurring.

Laparoscopic Tubal Ligation Pain

Tubal ligation is a surgical procedure intended to prevent the passage of the ovum into the uterus via the fallopian tubes. Once the ovum's passage is blocked, the female is no longer able to become pregnant. It has been estimated that there are one million tubal ligations performed annually in the United States (Tulandi, 1997).

The procedure is commonly performed through a subumbilical incision, with a direct-trocar insertion or Veress needle, followed by insufflation of the abdomen with carbon dioxide gas and insertion of accessory trocars. Once the fallopian tubes are identified, they are held in place with forceps and either cauterized, or occluded by compression with mechanical bands, clips, or rings.

There are several types of laparoscopic tubal ligations performed in this country. Three of the more common methods are Fallope rings, Filshie clips, and diathermy (cauterization of the fallopian tubes). The mechanical loop method is the one used most often at the site for the study. This technique uses a single ring on each fallopian tube causing a mechanical obstruction to the passage of ovum

Pain from laparoscopic procedures is multifactorial to include visceral, incisional, and from carbon dioxide insufflation of the abdominal cavity. This pain is often localized in the upper abdomen, lower abdomen, and back; however, there is also a phenomenon known as referred shoulder pain (Davis & Miller, 1988). Visceral pain is a direct result of manipulation of structures and tissues within the abdomen. Incisional pain is a direct

result of surgical incision to tissues. Studies have not addressed this type of pain specifically because it is perceived as being incidental (Cade & Kakulas, 1995; Rasanayagam & Harrison, 1996; White, Joshi, Carpenter, & Fragen, 1997). Incisional pain is characterized as sharp and localized to immediate area of the trocar insertion sites. The visceral pain generally subsides after the first twenty-four hours. Referred shoulder pain increases after twenty-four hours and can persist for three days or more. This referred shoulder pain has been shown to result from the insufflation of the abdomen with carbon dioxide gas used in the procedure (Dobbs, Kumar, Alexander, & Hull, 1987). The localization of pain to the shoulder is due to the excitation of the diaphragm and phrenic nerve. The amount of gas used is directly proportional to the postoperative pain reported (Wittels et al., 1998). Aspiration of gas at the end of the case has been shown to decrease this pain. Once the body has absorbed and removed the carbon dioxide from the person's system, the pain subsides.

Pain intensity associated with laparoscopic procedures varies depending on the specific surgery performed. A patient undergoing a diagnostic laparoscopic procedure has much less reported pain than those with a laparoscopic tubal ligation or cholecystectomy (Davis & Miller, 1988). No one drug has been found effective in controlling all forms of pain associated with laparoscopic procedures (Wittels et al., 1998).

Ketorolac has been studied in several laparoscopic procedures as a pre-emptive analgesic and found to be effective in some procedures (Cabel, Beeston, Embry, & Hurt, 1997). Ketorolac's benefits are realized several hours after administration. Given immediately prior to the surgical procedure, ketorolac will have a peak action in the postoperative period. However, it was shown to be less effective in decreasing

postoperative pain following laparoscopic tubal ligation (Edwards, Barclay, Catling, Martin & Morgan, 1991; Crocker & Paech, 1992; Shapiro & Duffy, 1994). This may in part be a result of the differences in pain experienced from the various types of laparoscopic procedures available for tubal sterilization. Of the three techniques popular in the United States, the Filshie clips are associated with the least amount of postoperative pain (Rioux & Yuzpe, 1997).

Pain Assessment Tools

An efficient, reliable, and sensitive pain measurement device with proven validity are characteristics any researcher desires in a physiologic instrument (Gift, 1989). Choosing a tool that can handle the difficult task of accurately measuring clinical pain continues to be problematic even today (McGuire, 1984). The subjective nature of pain continues to present a major obstacle in pain measurements. Recognizing this limitation, McCaffery (1979) primarily relied upon the patient's self-report when measuring pain. This reliance upon patient reporting of pain has proved unsatisfactory for many researchers and clinicians when there is a need for quick verification of their patient's experience (McGuire, 1988). A tool that effectively allows patients to communicate their pain experience to researchers is essential to any research project looking at postoperative pain. Additionally, such a tool produces valuable data for the researcher in their evaluation of patient outcomes.

The perfect pain assessment tool would quickly and accurately allow the patient to convey their pain and all its dimensions to the researcher. This data could then be interpreted by the researchers in a quick and easy manner enabling them to accurately

quantify the data. In order to select the appropriate pain tool for this study, it was necessary to review several tools in use today with their advantages and limitations.

Pain Assessment Tools Used Today

Visual Analog Scale (VAS): The VAS consists of a 10 cm line, sometimes 15 cm, anchored at both ends with descriptive terms indicating extremes of pain (Wewers & Lowe, 1990). Typical terms at the anchors might be, "no pain", and "the most pain you've ever experienced". Patients are asked to make a mark on the line that indicates their level of pain intensity. This mark is then measured and recorded. The VAS is a one-dimensional scale that measures pain intensity only. Both validity and reliability of the VAS have been evaluated (Wewers & Lowe, 1990). Test-retest methods for reliability found a high degree of correlation, range of 0.95 to 0.99. Validity of the VAS has been evaluated by a variety of methods. Experiments designed to test construct validity, discriminant validity, and criterion-related validity have given increased credibility to the VAS as a valuable tool of measurement (Wewers & Lowe, 1990).

The advantage of the VAS is that it avoids problems associated with language. Because very little language is used in the VAS, the vocabulary level of the patient is usually not an issue (Wewers & Lowe, 1990).

The biggest disadvantage of the VAS is that some patients have difficulty converting their pain to a mark on a line, thereby threatening the reliability of the tool (Dixon & Bird, 1981). Patients who view it in this way often fail to complete the VAS. For this reason the VAS has been criticized as too abstract compared with other scales. Secondly, the VAS must be administered in written form that involves two steps: the patient first makes a mark on the VAS, the researcher then measures the mark and records the

numeric value. This type of data collection has a higher risk of error associated with it as it may be measured or transferred incorrectly. Thirdly, Dixon and Bird (1981) found there was a tendency to estimate too high on the VAS and that its degree of reproducibility varied along its length. Patients in the immediate postoperative period may not be able to adequately see the chart and make an accurate mark along the line to indicate their true pain at that time. This could be attributed to the patient not having their glasses with them in the recovery room, to a residual anesthetic causing decreased visual acuity, residual interference with cognitive function, or decreased physical coordination. One final disadvantage of the VAS is that it is cannot be used to collect pain scores telephonically. This prevents its use as a follow-up pain evaluation by researchers using a telephone, which was a component of this study design.

Numerical Rating Scale (NRS): The NRS, described by Downie in 1978 as a linear scale consists of 11 numbers all in boxes in a linear arrangement. The patient is asked to rate his/her pain between 0 and 10 with "0" being no pain and "10" being the worst pain imaginable. The patient is then asked to put a mark in the box that corresponds to their current level of pain intensity. The NRS has been shown to be a reliable and valid pain tool in several experiments using the VAS for comparison (Briggs, Closs, & MPhil, 1999; Ferraz et al., 1990; Paice & Cohen, 1997). It is important to mention the existence of another commonly used version of the NRS, the NRS-101. The NRS-101 is nearly identical to the NRS except that when the patient is asked to rate their pain, a scale is used with numbers between 0 and 101, rather than between 0 and 10, in the same manner as the NRS. A visual linear row of boxes with corresponding numbers does not normally accompany the NRS-101 as it does in the NRS, otherwise the scoring is the same on the

two scales. A follow-up study (Jensen, Turner, & Romano, 1994) found that the correlation coefficients associated between NRS and NRS-101 was $r > 0.98$, and patients generally do not differentiate between the two scales.

The advantages of the NRS is that it is simple to administer, easy to score and a readily administered pain scale in both written and verbal form. With appropriate substitution of anchor words, it can be used with non-English speaking patients.

The disadvantage is seen in its use at extremes of age. The elderly occasionally have impaired cognition and the very young are frequently unable to either understand or communicate the concepts inherent in the NRS. For these populations, the NRS is ineffective (Flaherty, 1996).

Verbal Descriptive Scale (VDS): In 1948, Keele devised a pain scale consisting of five numerically ranked words describing pain intensity. He chose the words "none, slight, moderate, severe, and agonizing", and then administered this tool to a wide variety of his patients to establish reliability. Validity was established using patients with conditions known to cause pain and observing predictable increases and decreases with activity and time.

Today nearly all VDS [also called a Verbal Rating Scale (VRS)] use either Keele's identical descriptive words or very similar adjectives. The VDS effectively converts a subjective entity into quantifiable data useful to a researcher (Flaherty, 1996). Ohnhaus and Adler (1975) compared the VAS and VRS (VDS) and found a strong correlation between the two scales ($r = 0.81$, $p < 0.001$) with the VAS being more sensitive in detecting changes in pain level. However only six patients participated in this study, and care must be taken when interpreting the results.

Jensen, Karoly, and Braver (1986) compared six measures of pain, including the VAS, VDS and NRS. The study deemed three criteria as critical when judging a pain intensity measure: (a) ease of administration and scoring, (b) rate of correct response, and (c) evidence for the construct validity of a scale. Although Jensen (1986) stated all three scales met criteria, they emphasized the disadvantages of the VAS in its two-step scoring and its requirement to be administered in written form. In a follow up study, Jensen et al. (1994) looked at how many pain intensity levels were needed for adequate assessment. They discovered that when given a scale with 101 pain levels 98% of patients rated their pain in multiples of 5 or 10 on the 101-point scale. The 11-point NRS scale was strongly ($r > 0.99$) associated with the 101-point measure in the study. Jensen (1994) concluded that no advantage is gained with intensity measures over 11 levels. The investigators further maintained that measures with 6 measurement levels or less quickly loose their degree of sensitivity.

This research study required ease of administering and scoring pain intensity. Pain was evaluated for 48 hours postoperatively. The subjects in this study were chosen from an outpatient population necessitating the need for a tool that could be used during a telephone interview. The NRS is easily administered in both the verbal and written forms. In comparisons with the VAS, the NRS has been shown to be both reliable and valid ($r = 0.847$, $p < 0.001$), (Paice & Cohen, 1997). The age range of subjects in this study avoided the main disadvantage of the NRS, namely use in the extremes of age.

Controversy still exists as to whether the NRS generates ratio, interval or ordinal data. In a 1993 survey of anesthesia literature, Mantha, Thisted, Foss, Ellis, and Roizen (1993) found that approximately 50% had used parametric tests. Ludington and Dexter (1998)

suggested that NRS scores are ratio data because a score of zero represents a true zero (indicating complete absence of pain). Myles, Troedel, Boquest, and Reeves (1999) tested the hypothesis that VAS scores are a linear measure of pain; based on their findings they concluded that scores do have a linear property. Several other have argued in favor of treating NRS scores as ratio data (Dexter & Chestnut, 1995; Myles et al., 1999; Philip, 1990). Based on the literature, all NRS scores in this study were treated as interval data for purposes of statistical analysis.

Recent Studies Involving Dextromethorphan

Kawamata et al. (1998) studied postoperative pain and analgesic requirements in adult subjects undergoing tonsillectomy after receiving a preoperative dose of dextromethorphan. Using a double-blinded, placebo-control, with random assignment to groups, thirty-six ASA physical status I patients were assigned to one of three groups. One group received oral placebo (starch pill), one group received 30 mg of dextromethorphan orally, the third group received45 mg of dextromethorphan orally. Anesthesia was standardized for all three groups to help control for confounding variables. Pain scores were recorded using a self-rating VAS consisting of a 100-mm horizontal line without graduation, and end points of "no pain" and "worst possible pain". A two-way analysis of variance for repeated measures, followed by Fisher's protected least significant difference test at each time point was used to analyze VAS scores. Two scores for pain were recorded at each data collection point, one while at rest with no pharyngeal movement, and another while swallowing 50 ml of water. Kawamata et al. (1998) concluded that there was no significant difference in VAS scores between the dextromethorphan groups ($p > 0.05$). However when compared to placebo, the 30 mg

dextromethorphan group had significantly lower pain scores, except on the second and third postoperative day ($p < 0.05$). The 45 mg dextromethorphan group recorded significantly lower VAS scores during all seven days that scores were collected.

A Kruskal-Wallis test followed by the Mann-Whitney U-test were used to compare total analgesic doses between all groups over the seven-day period. Total dose of analgesic were significantly lower in both dextromethorphan groups compared to the placebo group (Placebo = 200 mg, DM 30 = 100 mg, DM 45 = 50 mg) ($p < 0.05$). Total doses of analgesics are ratio data, with an absolute zero, and equal intervals between numbers. It is unclear why these investigators chose to perform a nonparametric test on this data.

Kawamata et al. (1998) were able to show significantly decreased pain scores and analgesic requirements for seven-days postoperatively following a single dose of oral dextromethorphan. While both doses of dextromethorphan significantly reduced pain compared to placebo at most time points, only the 45 mg dose was able to reduce pain even while swallowing. This might be explained by the differences in doses, with 45mg being more effective at preventing "wind-up" by interfering with a larger number of NMDA receptors prior to surgical stimulation. The lower dose of 30 mg may not have provided sufficient serum levels prior to surgical stimulation to prevent activation of as many NMDA receptors. This interference with fewer NMDA receptors would also explain the inability to detect a significant difference in pain scores between the 30 mg dextromethorphan group and placebo at postoperative days two and three. After the first postoperative day, patients might be expected to experience more pain as they return their normal activities, talking more, and progressing from a liquid diet to one containing more

solids. It is possible that 30 mg of dextromethorphan only interfered with enough NMDA receptors to show significance once the level of pain had decreased from the initial postoperative pain levels. This would be consistent with findings from other studies showing a significant decrease in pain scores only after twenty-fours postoperatively (Chia et al.,1999; Henderson et al., 1999).

A similar study by Rose et al. (1999) examined dextromethorphan given to children six to twelve years of age undergoing tonsillectomies and came to the conclusion that no reduction in pain was achieved. They designed their study as a double-blind, placebo-controlled prospective study utilizing random assignment to groups. Anesthetic agents and doses were standardized for all study participants on a milligram per kilogram basis. Calculated dosages for oral dextromethorphan were based upon milligrams per kilogram of body weight to account for the large variance in body weights for children in this age range. The aim of their study was to determine whether administration of oral dextromethorphan preoperatively improved postoperative analgesia, reduced opioid consumption, and improved parental satisfaction with postoperative pain management during the first 24 hours following surgery.

One assumption of their study was that total morphine use would be 0.16 ± 0.05 mg/kg intravenous before post anesthesia care unit (PACU) discharge in children undergoing tonsillectomy. A sample size of 16 was calculated using power analysis to be able to detect a 25% reduction in morphine consumption compared to placebo with 80% power and $\alpha = 0.05$. To compensate for attrition, they decided to recruit 20 patients per group. The three groups used in this study consisted of Group I receiving 0.5 mg/kg dextromethorphan, Group II received 1.0 mg/kg dextromethorphan and Group III

received a placebo. Two pain scales were used for collecting pain scores, the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and a Visual Analog Scale (VAS). CHEOPS scores were collected every 15 minutes in the recovery room until discharge to the Day Surgery Unit (DSU). Once in the DSU, pain scores were collected every 30 minutes until discharged to home using a VAS consisting of a 10 cm line with anchors of 0 indicating "no pain" and 10 indicating "worst imaginable pain". A 24-hour VAS score was obtained by telephone along with a parental satisfaction (yes/no) with their child's postoperative analgesia. Information on total amount of morphine (mcg/kg) received in the recovery unit was collected and compared using analysis of variance (ANOVA) for interval data. No significant difference in analgesic use was found between any of the three groups (44 ± 7, 49 ± 7, 41 ± 7 mcg/kg, $p = 0.75$). When mean doses of codeine administered in the DSU were compared, again no difference could be detected.

Several differences in this study may account for the lack of analgesic sparing qualities and reduction in pain scores compared to results obtained from Kawamata et al. (1998) study. First, for ethical reasons the researchers decided they could not withhold perioperative analgesic administration to these children as that was the standard of care for their facility. Kawamata et al. (1998) did not give their subjects any other analgesics before or during the procedure. This intraoperative administration of opioids to children in the Rose et al. (1999) study may have masked any differences in the immediate postoperative period. Secondly, this study only followed the children for 24 hours, a period of time when the postoperative pain is presumably greatest. Perhaps following the children for a longer period of time would have been able to detect a statistically significant difference. Previous studies have only found a significant decrease in pain and

analgesic requirements after 24 hours. While the authors did choose to use the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), which is designed for children and has been shown to be both valid and reliable, assessing pain in children presents unique challenges. Other variables not modifiable at the NMDA receptor can contribute to pain or pain behaviors in children including parental separation, anxiety, and fear.

Henderson et al. (1999) examined dextromethorphan's effect on postoperative pain in women following hysterectomy. Using a double-blind, placebo-controlled study with random assignment to groups they gave one group an oral placebo capsule (lactose) preoperatively and three times per day for two days. The experimental group received 40 mg of dextromethorphan orally before surgery, and then 40 mg three times per day for two days using the same administration times as the placebo group. All subjects received a standardized anesthetic to control for extraneous variables and included intraoperative administration of intravenous morphine (0.15 mg/kg). At the end of the procedure, the abdominal wound was infiltrated with 15 ml of 0.5% bupivacaine. A previous study at their hospital indicated a mean total postoperative morphine consumption of 34 mg $\pm$ 20 mg/day was a normal value for patients undergoing abdominal hysterectomy (Espinet, Henderson, Faccenda, & Morrison, 1996). Using this information, the authors decided that a 40% reduction in morphine use would be clinically significant resulting in less than 20 mg/day usage. With α set at 0.05 and using a power of 90%, they determined group size (N = 48). Fifty patients were subsequently enrolled with 47 patients completing the study. Comparison of demographic data using Student's t-test failed to show any statistical difference between the two groups. A 100 mm VAS scale was used to measure

pain at rest and on movement at 4, 24, 48, and 72 hours; analgesic consumption was also recorded for the entire 72-hour period.

Following surgery, morphine was administered via a patient controlled analgesic (PCA) pump. The morning following surgery the PCA pump was replaced with on demand oral analgesic (Diclofenac 50 mg orally every 8 hours on request). Median pain scores for the two groups were compared using Mann-Whitney analysis with Bonferroni correction with $p < 0.05$ considered significant. Median pain scores at rest were lower for the dextromethorphan group at all times, but only reaching statistical significance at 48 hours (15 vs. 22), and 72 hours (9 vs.18). The sums of all resting pain scores covering the three-day period were also significant (median score 75.5 vs. 124.5, $p < 0.01$). No significant difference was detected between the groups on pain measurement with movement at any time point. Morphine consumption in the first 24 hours did not reach statistical significance but was higher in the placebo group (1.5 vs. 1.1 mg/hr, $p = 0.054$). Over the next 48 hours, they found a significant decreased use of codydramol (10.6 vs. 15.1 tablets, $p < 0.05$), but not in diclofenac usage, (189.6 mg $\pm$ 111.3 vs. 218.2 mg $\pm$ 130.5).

Despite using multiple doses of dextromethorphan, including preoperatively and postoperatively, Henderson et al. (1999) were unable to show a statistically significant decrease in pain scores during the first twenty-four hour period. Pain stimuli in the immediate postoperative period are characterized as more intense and gradually decrease over time in the postoperative period. This is consistent with the action of dextromethorphan acting at the NMDA receptor to prevent activation, preventing the phenomenon of hyperalgesia or "wind-up", but not interfering with the AMPA receptor.

This is one possible explanation why dextromethorphans' effect is not seen until the surgical pain decreases to a level where the impulses transmitted via the AMPA receptor have decreased sufficiently to be distinguished from the placebo group.

Grace et al. (1998) looked at postoperative pain scores and analgesic consumption in patients undergoing laparotomy. They also explored whether dextromethorphan had any effect on intraoperative morphine consumption. To perform their power analysis, they assumed a 24-hour average morphine consumption of 70 mg ± 27 mg. A reduction of 40% average use was determined to be of clinical significance for this study. Setting α at 0.05, 18 patients in each group were required to achieve 90% power. To allow for attrition, 40 patients were enrolled and 37 completed the study. Patients were randomly assigned to one of two groups, one receiving oral placebo the night before surgery and again one hour before surgery. The second group received 60 mg of dextromethorphan orally at the same time points. Both placebo and dextromethorphan were supplied in identical looking capsules. A double-blinded design was used for administering the capsules. Duration of surgeries was not statistically different; dextromethorphan 146 ± 44 minutes, placebo 164 ± 52 minutes. Morphine doses were recorded for the two group in the recovery room, at four hours and at twenty-four hours postoperatively. Statistical significance was not achieved at any point; mean recovery room morphine use plus and minus standard deviations were reported (12.1 mg ± 1.8 vs. 10.9 mg ± 1.8, $p = 0.63$), first four hours (12.7 mg ± 1.2 vs.15.9 mg ± 2.9, $p = 0.21$), and twenty-four hours (61.8 mg ± 6.3 vs. 76.4 mg ± 10, $p = 0.24$). When they compared means for total morphine used, no statistical significance could be found (91.5 mg ± 7.6 vs. 100.4 ± 11.7, $p = 0.53$). They also looked at intraoperative morphine consumption required to maintain the patient's

blood pressure and heart rate within 20% of baseline. A statistically significant difference was detected between the groups, with the dextromethorphan group requiring less morphine (17.6 mg ± 1.4 vs. 13.1 mg ± 1, $p = 0.012$). Pain scores were collected at these points, while at rest and with activity; no statistically significant difference between groups was found in either.

The authors concluded that intraoperative but not postoperative pain and morphine consumption are reduced by preoperative administration of dextromethorphan. This despite the fact that they used more than twice the dose of dextromethorphan as compared to Kawamata et al. (1998), which did show a decrease in postoperative pain and analgesic use after a single preoperative dose. Grace et al. (1998) failed to account for the time required for capsules to dissolve once ingested. Depending on gastric conditions, including volume and pH, gel capsules can require thirty minutes or more to dissolve. Following oral ingestion of non-encapsulated dextromethorphan, serum levels take as long as two-hours to peak. This makes it very unlikely that sufficient time had elapsed from time of ingesting the dose one-hour before surgery for it to be of any benefit in preventing "wind-up". This would explain why no significant difference in pain scores and analgesic use could be detected following surgery. Residual serum levels of dextromethorphan from the dose taken the evening before surgery might explain the decreased need for intraoperative morphine in this study.

One other difference between this study and that of Kawamata et al. (1998) is that Grace et al. (1998) chose to study pain and analgesic use in patients presenting for invasive abdominal surgeries which are associated with more pain. Kawamata et al.

(1998) only used adults presenting for tonsillectomy, a procedure associated with much less pain following surgery.

Wu et al. (1999) explored whether dextromethorphan reduces postoperative pain and if timing of administration had an effect. Participants were selected from a convenience sample of patients presenting for laparoscopic cholecystectomy. The authors used three groups: control, 40 mg dextromethorphan injection preoperatively, and 40 mg dextromethorphan injection postoperatively, (N = 90). While a double-blinded design was not used for the administration of the control or dextromethorphan, all assessments were made on a double-blinded basis. All subjects received a standardized general anesthetic that included 2 mcg/kg of fentanyl for induction. No additional opioids were given during the surgery. Meperidine (1 mg/kg IM) was used for postoperative pain relief when requested. Pain scores were collected using an eleven point VAS, (0 = no pain, and 10 = severe, intolerable pain). Statistical analysis of demographic data did not reveal any significant difference between the three groups.

Total meperidine requirements were analyzed using a one-way ANOVA comparing means ± standard deviations. Meperidine requirements in the control group were 90.7 ± 65.2 mg compared to 77.5 ± 69.6, and 20.0 ± 24.1 mg for the postoperative administration and preoperative administration groups respectively ($p < 0.00001$ preoperative group versus postoperative group, and $p < 0.0000001$ when comparing preoperative administration to control). When VAS scores were compared, the control and postoperative administration groups had significantly higher means relative to subjects receiving dextromethorphan preoperatively; control (6.0 ± 1.1), postoperative (6.0 ± 1.1), and preoperative (4.0 ± 2.2, $p < 0.0001$ compared with postoperative group,

and $p < 0.000001$ compared to control). The authors concluded that preoperative but not postoperative administration of dextromethorphan decreased VAS scores and total meperidine requirements compared to the control group.

Wu et al. (1998) was able to demonstrate that only the pre-emptive administration of dextromethorphan is capable of decreasing postoperative pain and analgesic requirements. This gives further evidence to the concept that once the NMDA receptor has been activated dextromethorphan is no longer effective.

Results from studies on the effectiveness of dextromethorphan in reducing postoperative pain scores and analgesic requirements have yielded inconsistent results. However, many of these inconsistent results can be explained by the study design employed. Those that have investigated administering preoperatively versus postoperatively have shown pre-emptive administration to be more effective (Helmy & Bali, 2001; Henderson et al., 1999; Kawamata et al., 1998; Wu et al., 1999) compared to postoperative administration (Wu et al., 1999). This is consistent with what is known about the NMDA receptors role in the transmission of pain. Some studies have used a single preoperative dose of dextromethorphan while others have investigated whether a multiple dosing regimen was more effective in decreasing postoperative pain scores and analgesic use. Studies using a single preoperative dose have been able to demonstrate a significant reduction in pain scores and analgesic (Chia et al., 1999; Helmy & Bali, 2001; Kawamata et al., 1998; Wu et al., 1999). However some studies using a single dose have not been able to demonstrate a significant decrease in pain or analgesic use (Rose et al., 1999; Wadhwa, Clarke, Goodchild, & Young, 2001). Those that did not find significance either used a smaller dose or did not look at pain scores and analgesic use past twenty-

four hours postoperative, a time when most studies have found significance. Different doses have been tried in an effort to determine the most effective dose but have not conclusively shown what dose is most effective (Weinbroum et al., 2001).

Given the positive results in some studies, and what is now known about the role of the NMDA receptor in the potentiation of pain, further studies are indicated. Dextromethorphan is an inexpensive drug with few side effects that shows promise in improving patient pain control and satisfaction while decreasing analgesic use. This opioid sparing effect may also have the potential to decrease associated side effects.

CHAPTER III

Methodology

This was a prospective, double-blind, randomized, pilot study comparing the difference between dextromethorphan and placebo in preempting postoperative pain in patients presenting for ILBTS. This chapter describes the population, sample, setting, instrumentation, study design, procedure for data collection and analysis, and protection of human subjects.

Population, Sample, and Setting

The sample population was derived from female patients electing to undergo ILBTS. The setting was Tripler Army Medical Center (TAMC), a 256-bed regional medical center, with thirteen surgical suites, located on the island of Oahu in the state of Hawaii. TAMC provides all major surgical services (including gynecological) for members of all branches of the United States military (Army, Air Force, Navy, Marine, & Coast Guard). This includes: (1) active duty military and their dependent family members, (2) military retirees and their dependent family members, and (3) Veteran's Affairs (VA) eligible patients. In addition, TAMC provides referral services to all other military facilities in the Pacific region. Lastly, TAMC is a teaching facility that provides residency training in a variety of surgical specialties, to include obstetrics and gynecology as well as training nurse anesthetist.

Subjects were screened and a convenience sample consisting of those meeting inclusion criteria were invited to participate in the study. Inclusion criteria consisted of (a) women of at least 18 years of age presenting for elective ILBTS from January 6, 2001

to May 1, 2001, (b) American Society of Anesthesiologists (ASA) physical status I or II, and (c) at least six weeks postpartum.

Exclusion criteria (Appendix B) were based on the associated adverse interactions of other drugs with dextromethorphan. Prospective patients were excluded for the following reasons: (a) a history of allergy to dextromethorphan, (b) current use of monoamine oxidase inhibitors (MAOIs), (c) a history of psychiatric illness or substance abuse, (d) subjects who were currently taking analgesic medications, (e) non-English speaking subjects, or (f) a clinical indication for using succinylcholine with induction or placement of an oral gastric tube for stomach decompression.

Using power analysis with α set at 0.05 and β at 0.80, 25 subjects were needed in each group to allow detection of a medium effect size in terms of a reduction of pain scores. An initial pilot study consisting of six patients in each group was planned before proceeding with the full study.

Study subjects were randomly assigned to one of two groups. Group I consisted of patients receiving oral dextromethorphan 60 mg preoperatively. Group II received an oral placebo preoperatively.

Instrumentation

An 11 point verbal Numeric Rating Scale (NRS) was used as the tool for measurement of postoperative pain reported by the patients. In their published guidelines for measuring acute pain, The Agency for Health Care Policy and Research has recommended using the NRS (Dalton & McNaull, 1998). Previous studies have consistently shown a strong correlation between the Visual Analogue Scale (VAS) and the NRS (Jensen et al.,1986; Ohnhaus & Adler, 1975; Woodforde & Merskey, 1972). The

NRS is considered to have good reliability and construct validity when patient self-report is used as the method of data collection (Jensen et al. 1986). Additionally, the NRS was previously established in the unit protocols for the Post Anesthesia Care Unit and the Ambulatory Surgical Center in the facility where the study was conducted. This fostered the support received from the nursing staff that assisted with data collection. In addition, the investigator designed demographic data collection sheet (Appendix C) was used. This tool allowed data collection to be consistent even when collecting data telephonically.

The Principal Investigator, or one of the Surgical Admission Center (SAC) nurses used a standardized script when giving the initial explanation of the NRS to study subjects. This was done either telephonically, at least one day before surgery, or during the preanesthesia interview. The subjects were asked to give a return verbal understanding of the tool. In order to establish a baseline on each study participant, the first NRS score was collected the morning of surgery prior to any interventions.

All study participants were asked to rate any pain they were having using the NRS. All of the personnel in the SAC and PACU received training on the NRS prior to the start of the study. The subjects were asked to rate their pain using the NRS seven more times. The times were as follows: (a) immediately upon arrival to PACU, (b) 15 minutes after arrival to PACU, (c) one hour after surgery or discharge from PACU (whichever came first), (d) four hours after surgery, or discharge home (whichever came first), (f) six hours after surgery, (g) 24 hours following surgery, and (h) 48 hours following surgery.

Procedure for Data Collection

The following procedures were used for data collection:

Preoperative Enrollment

1. Prior to the start of the study, a pharmacist was assigned to assist the investigators with any pharmacy-related issues. An initial goal prior to commencement of data collection was the design of a packaging system that would allow the study to be double-blinded with regard to the drug under investigation. The oral dextromethorphan was packaged in a 15 cc syringe in a fructose medium (60 mg in 15 cc) and the placebo was easily packaged in 15 cc syringes of fructose only; no difference in taste was discernible to three pharmacy personnel. Additionally, one of the pharmacists assisting the investigators developed a computerized medication order set, formulated a pharmacy budget, and produced a study drug information teaching packet with access on the facility's intranet website. All personnel involved in the handling of the study drugs were required (JCAHO standard) to read the information in the study drug information packet and were required to take a product knowledge quiz.

2. All patients scheduled for ILBTS at TAMC between January 6, 2001 and June 1, 2001 were contacted by the Principal Investigator, at least one day before surgery. Potential candidates for the study were identified on the facility's intranet surgery scheduler. Potential subjects were contacted at home by telephone, or if possible at their preoperative anesthesia interview in the SAC. Those candidates meeting the inclusion criteria, and not falling under exclusion criteria were asked to participate in the study.

3. When possible, written, informed consent (Appendix D) was obtained from subjects at their preanesthesia interview. Otherwise, verbal consent was obtained

telephonically, and then written informed consent was obtained on the day of surgery in the SAC.

4. After obtaining subjects' consent, a medication order set was sent to the pharmacy one day in advance of surgery; in addition, a telephone follow up to pharmacy was used to verify receipt of the order. The pharmacist on duty randomly assigned the subjects to one of two groups. This was accomplished using a standard table of random numbers.

5. On the day of surgery, the study drug packet was picked up in the pharmacy, and placed the packet along with the data collection sheet, volunteer agreement affidavit, and the home questionnaire (all forms were printed on a lime green sheet) on the subject's chart in the SAC.

6. The subjects' charts were labeled with a green "tubal study patient" to indicate participation in the study.

7. Upon admission to the SAC written, informed consent (if not already done) was obtained from the subjects by one of the staff nurses or investigator. The NRS was once again explained to the subject with a return verbal demonstration of the tool.

8. The subjects were asked to rate any preoperative pain using the NRS, and this was recorded along with location of pain, age, weight, height, and ethnicity on the data collection sheet.

9. Approximately one hour prior to induction, the subjects were given either dextromethorphan 60 mg or an oral placebo. The investigator, as well as the subjects, were blinded as to which medication was given.

10. Upon arrival in the preoperative holding area, an intravenous line was established with an infusion of Lactated Ringers as the maintenance solution.

11. Intravenous midazolam (1-5 mg) was administered for anxiolysis.

12. The subjects were then transported to the operating room.

Standardized Anesthetic

Induction

1. Monitoring devices were applied to include: (1) continuous electrocardiogram (ECG), (2) noninvasive blood pressure cuff, (3) precordial stethoscope, (4) pulse oxymeter, (5) oxygen analyzer, (6) capnograph, (7) peripheral nerve stimulator, and (8) temperature monitor.

2. The subjects were preoxygenated/denitrogenated with 100% oxygen for 2-3 minutes.

3. Fentanyl 50-150 mcg intravenously was given to attenuate the sympathetic response to intubation.

4. Propofol 2-3 mg/kg was administered intravenously for induction of anesthesia.

5. The ability to manually ventilate was established prior to paralysis.

6. Neuromuscular blockade was achieved using rocuronium 0.6-1.2 mg/kg intravenously.

7. The subjects were intubated with a #7 oral endotracheal tube by direct laryngoscopy.

Maintenance

1. The inspired oxygen fraction was maintained at a minimum of 0.30 with a mixture of air and oxygen.

2. Anesthesia was maintained with an end-tidal concentration of isoflurane (0.5-3%) titrated to effect.

3. The autonomic response to surgical stimuli was attenuated with inhaled agent and fentanyl 25-50 mcg, titrated to effect. Total fentanyl administration including the induction dose was limited to 5 mcg/kg/hr.

4. Dolasetron 12.5 mg was given intravenously before emergence as an antiemetic.

Emergence

1. Neostigmine .04-.08 mg/kg and glycopyrrolate 0.01- 0.02 mg/kg (equivalent volumes) were given intravenously for reversal of neuromuscular blockade.

2. The subjects were extubated in the operating room once extubation criteria had been met. These included: spontaneous respirations, return of protective airway reflexes, and the ability to follow commands.

3. The subjects were then transported to the PACU with supplemental oxygen provided via a simple facemask.

Postoperative Assessment

1. Upon arrival to the PACU, subjects were asked to rate their pain using the NRS.

2. The PACU nursing staff had the subjects evaluate their pain using the NRS at 15 minutes after admission, and again at one hour or at discharge from the PACU.

3. The subjects' pain was subsequently evaluated using the NRS at four hours after surgery, or discharge to home, whichever came first.

4. The subjects were given a take-home questionnaire, along with a self-addressed stamped envelope to score their pain at six hours, 24 hours and, 48 hours postoperatively (Appendix E).

5. While in the PACU, rescue analgesics and antiemetics were administered per unit protocols with the exception of withholding intravenous ketorolac. While in the SAC, rescue analgesics and antiemetics were administered per unit protocols.

6. Approximately 48 hours after surgery, each subject was contacted by telephone to assess their postoperative course, and to obtain NRS scores for the 6, 24 and 48 hour data collection points.

Protection of Human Subjects

Approval by the Scientific Review Committee and the Human Use Committee of TAMC were obtained prior to enrolling any subjects into the study (Appendix F). Also, the Committee for the Protection of Human Subjects (CPHS) at the University of Texas at Houston Health Science Center granted approval.

Subjects were verbally counseled prior to surgery, and consent was obtained prior to entering the patients in the study. Subjects were informed that their participation was entirely voluntary, and that they could withdraw from the study at any time without affecting the care they would receive. The purpose of the study, as well as risks, benefits, and the subjects' time commitment were discussed as part of the consent agreement.

Confidentiality was maintained as recommended by Polit and Hungler (1995). Numbers were assigned to each subject to maintain confidentiality. This number was also used when entering subject data into a computer for tracking and analysis. This information was kept secure in a database (on floppy computer diskette kept in a locked file, in a locked room). Information linking individual subjects' data with their name was maintained separately, and was only accessible to the faculty and the investigator. The pharmacy also maintained a log, which cross-referenced subjects names and register

numbers with study packet numbers in a locked file. This information was readily available to the investigators in case of a medical emergency.

The only information being disclosed is aggregate data generated in this study, no individual data are being reported. Subjects who indicated a desire to obtain the final results will be sent a copy of a summary after thesis defense. Addresses maintained for purposes of mailing results are maintained separately from the data in a locked file, and will be destroyed after results are sent to the participants following thesis defense.

Study Design

This was a prospective, randomized, double-blind pilot study testing the pre-emptive effect oral dextromethorphan on postoperative pain and total opioid administered postoperatively.

Internal Validity

One threat to the internal validity included selection bias implied by the use of a convenience sample. Randomization to group assignment was used to impart some degree of equalization between groups (Polit & Hungler, 1995). All staff that were used in data collection were given identical training; also a scripted dialog to use with the subject was employed to control for errors in instrumentation. The six-hour, 24 hour and 48 hour NRS scores were obtained by use of a take-home questionnaire and telephone follow up at 48 hours. Subjects were educated on the importance of the follow up telephone call and confirmed an accurate phone number for contacting them in an effort to minimize attrition. The take-home questionnaire was printed on lime colored paper to assist with easy identification among all the other perioperative forms the subjects were given to take-home. A self-addressed stamped envelope was attached to the questionnaire

so the participants could conveniently return-mail the questionnaire following completion.

Other threats to internal validity during this study included unanticipated changes in the surgical procedure, anesthetic protocol violation, inability to provide data due to excessive postoperative sedation, inability to reach the subjects 48 hours after surgery by telephone, or failure to return the home questionnaires. This threat to internal validity was addressed by standardizing the study protocol to include the surgical procedure, anesthesia, and all medication the patients received. In an attempt to minimize attrition caused by the inability to obtain six hour, 24 hour and 48 hour NRS scores, patients were reminded about the importance of returning the written questionnaire. During the follow up telephone call, NRS scores were collected and subjects were reminded of the importance of returning the questionnaire.

A double-blind study design was employed to help minimize the Hawthorne effect (Polit & Hungler, 1995). A scripted dialog with the subjects was used in an effort to control for effect any differences between investigators. The data collection tool was detailed in an effort to allow for exact replication, decreasing the chance of experiencing an error in measurement.

Data Analysis

Demographic data was analyzed using descriptive statistics, Chi-Square (ethnicity), and Student's t-test (age, BMI, height, weight, length of surgery, elapsed time following drug/placebo administration until direct laryngoscopy/incision/occlusion of first tube).

First, slopes for individual subject data NRS scores were calculated, then the mean of the slopes for each group calculated. A one-way ANOVA was then used to compare the means of the slopes for the two groups.

A difference was considered significant with $\alpha \leq 0.05$. Data was analyzed using JMP® statistical software version 4 (SAS institute). A careful review and analysis of the data was performed with the help of a statistician.

Instrumentation

The Numeric Rating Scale is an instrument used to measure the patient's perception of pain. The scale is 0 to 10 with "0" being "no pain" and "10" being "pain as bad as you can imagine". The validity of the test was originally assessed using patients suffering from various types of cancer (Paice & Cohen, 1997). This scale is widely used in health care for rating pain on a regular basis and is accepted to be standard of practice at many facilities (Paice & Cohen, 1997). This scale has been studied independently and compared to analgesic usage. The numeric rating scale was found to be consistent with the amount of pain medication used.

The final tool recorded the amount of analgesic used by the patient in the PACU, SAC, and taken at home after discharge. Following discharge a telephone interview was used to collect the information 48 hours following discharge.

Procedure for Data Collection

This study design utilized 8 data collection points with the first collected in the surgical admission center prior to receiving any interventions. This data point represents baseline for comparing the individual patient with themselves after the procedure. The second data collection point occurred immediately upon arrival in the PACU. The third

data collection point occurred at 15 minutes after arriving in the PACU. The fourth occurred at one-hour postoperatively, and the fifth at four hours postoperatively. A take-home questionnaire was used to obtain the sixth, seventh and eighth data collection points at six hours, 24 hours and 48 hours postoperatively, respectively. Included in the take-home questionnaire was information on total dose of analgesic required for pain as well as qualitative data on each subjects' perioperative experience. Prior to beginning the study, subjects were provided with information how to record pain using the NRS, with reinforcement prior to discharge.

Timeline

June 2000	Proposal presentation
January 2001	Approval by the Tripler AMC Institutional Review Board
January 2001	Approval by the University of Texas Houston Health Science Center
January 2001	Begin data collection
June 2001	Complete data collection
July 2001	Data analysis, complete results and discussion sections
August 2001	Present research to American Association of Nurse Anesthetists during annual convention
September 2001	Thesis defense
October 2001	Final submission of thesis
December 2001	Graduation

Budget

The anticipated costs of office supplies and reproduction of the thesis was $400.00. Additional fees for binding of the thesis were estimated at $350. The costs for travel and

presentation of the thesis was estimated at $2000. The Army incurred all expenses for the study drug, supplies and costs of preparing the thesis. The overall budget for this study was estimated at $2750.

Chapter IV

Analysis of the Data

The purpose of this study was to determine whether or not the pre-emptive administration of oral dextromethorphan decreased postoperative pain scores in female patients presenting for ILBTS with general anesthesia when compared to a placebo. This chapter compares the two groups with regard to demographic characteristics and research findings. This investigation had two hypotheses: (a) there would be a difference in reported postoperative pain, (b) there would be a difference in the amount of opioid administered postoperatively. Results obtained in this study support both hypotheses; there was a difference in reported postoperative pain scores in patients undergoing ILBTS who pre-emptively received 60 mg of dextromethorphan orally versus oral placebo. And ILBTS patients pre-emptively receiving 60 mg of dextromethorphan orally had a decreased requirement for postoperative analgesics compared to those receiving an oral placebo.

Description of the Sample

Sixteen women presented for elective ILBTS during the six-month data collection period; the final sample consisted of 14 ASA physical status categories I and II patients. Data collection ended after determining that viable data had been obtained from the 14 subjects. Subject attrition was related to the following. Two prospective subjects chose to not participate in the study (see Table 1). No subjects were lost to attrition during the study. Therefore, the rate of capture was 87.5% for the patients who presented for ILBTS during the data collection period, with 100% of enrolled subjects completing the study.

Table 1

Convenience Sample Capture Data (N=14)

Exclusion Criteria for Patients Not Enrolled in Study	Frequency
Does not understand English	0
Less than 18 years old	0
Current use of MAOIs	0
History of psychiatric illness	0
Less than six weeks postpartum on the day of surgery	0
Clinical indication for intubation requiring succinylcholine	0
Patient refusal	2
Total	2

Inpatient pharmacy personnel assigned study subjects to one of two groups using a table of randomization. Group I received 60 mg dextromethorphan orally in the SAC (15 ml lactose carrier). Alternately, Group II received an oral placebo (15 ml lactose only) in the Surgical Admission Center (see Table 2). The investigator, study participants, and nursing staff who assisted with data collection were blinded to the actual substance given to the patients.

Demographic data was analyzed using descriptive statistics, Chi-Square (ethnicity), and Student's t-test (age, BMI, height, weight, length of surgery, elapsed time following drug/placebo administration until direct laryngoscopy/incision/occlusion of first tube). NRS scores were analyzed by first calculating slopes for individual data sets and then taking the mean of the slopes for each group which were then compared using a one-way ANOVA.

Demographic data was compared between the two groups looking for homogeneity of characteristics to include age, height, weight, BMI, ethnicity, and ASA classification (Table 2). No category approached statistical significance indicating a successful process of randomization of subjects assigned to each group.

Table 2

Demographic Data Comparing the Two Groups (N=14)

Demographic Data	Group I (n = 8)DM	Group II (n = 6) Placebo	Probability
Age (years)	30.50 ± 6.63	33.50 ± 4.86	0.70
Height (cm)	166.25 ± 13.95	163.75 ± 5.00	0.58
Weight (kg)	72.00 ± 9.85	69.00 ± 5.43	0.29
Body Mass Index	25.30 ± 5.81	24.85 ± 2.23	0.90
Ethnicity			
Caucasian	5 (36%)	5 (36%)	N/A
African-American	2 (14%)	1 (7%)	N/A
Asian/Pacific Islander	1 (7%)	0 (0%)	N/A
ASA Classification			
I	4 (28.6%)	3 (21.4%)	
II	4 (28.6%)	3 (21.4)	
Nausea in hospital	3 (21.4%)	4 (28.6%)	0.32
Received antiemetic(s)	2 (14.3%)	2 (14.3%)	0.76

Note: Values for continuous data are mean plus or minus one standard deviation. The numbers are frequencies referring to the actual subjects.

Compared variables for the surgical procedure and anesthesia were also similar between the two groups (Table 3). There were no statistically significant differences in

the total doses of fentanyl, propofol, rocuronium, isoflurane, neostigmine and robinol; this is attributed to strict adherence to established protocol.

Table 3

Surgical Procedure and Anesthetic Variables (N = 14)

Variables	Group I (n = 8)	Group II (n = 6)	Probability
Elapsed time until direct laryngoscopy following oral/placebo drug (min)	61.88 ± 3.21	62.00 ± 3.71	0.98
Elapsed time until incision following oral/placebo drug (min)	85.88 ± 7.32	90.33 ± 8.45	0.70
Elapsed time until first tube occluded after oral/ placebo drug (min)	102.13 ± 6.07	100.67 ± 7.00	0.73
Total surgery time (min)	37.00 ± 3.31	31.33 ± 3.82	0.35
Total PACU time (min)	92.50 ± 11.92	88.33 ± 13.76	0.82
Total postoperative time until discharge (min)	256.25 ± 31.42	256.67 ± 36.28	0.99
Total intraoperative fentanyl used (mcg/kg)	3.73 ± 0.30	3.85 ± 0.34	0.80
Total rescue morphine (mg)	5.94 ± 2.38	8.33 ± 2.75	0.60

Note: Values for continuous data are means plus or minus one standard deviation.

There were no significant differences following pre-emptive medications or placebos for elapsed times until direct laryngoscopy, surgical incision, or occlusion of tubes using Falope Rings. Length of surgery was also similar for the two groups. Two patients in Group I and two patients in Group II received meperidine postoperatively. Morphine equivalents were calculated (meperidine 10 mg = morphine 1 mg) in order to complete

statistical analysis (Stoelting, 1999). One subject in the dextromethorphan group had her fallopian tubes occluded by means of bipolar electrocautery; all other study subjects had their fallopian tubes occluded by Falope rings. Even though electrocautery is associated with more postoperative pain, this patient was included in the study. Lastly, none of the study participants were admitted overnight.

Findings

Data Analysis

The tested hypotheses state the following, patients who receive a pre-emptive dose of dextromethorphan 60 mg orally will have a difference in postoperative pain scores, and a difference in postoperative opioid usage compared to patients who received an oral placebo. Data were collected and documented by blinded observers using a preprinted data collection tool (Appendix C). Despite in-service training for all PACU staff prior to initiating the study, two patients in each group received intravenous meperidine while in the PACU contrary to study protocols. Because meperidine administration was evenly distributed between the two groups, and the amount given was not statistically different ($p < 0.35$), these patients were kept in the study. Demerol was converted to morphine equivalent units for statistical analysis, 10 mg meperidine = 1 mg morphine (Stoelting, 1999). The use of intravenous ketorolac for postoperative pain was also excluded from study participants. Ketorolacs' interference with the inflammatory process would have added a confounding variable to the study making it difficult to attribute any reduction in pain or analgesic requirements to the effects of dextromethorphan.

Total dosage of intraoperative fentanyl was not statistically different between the two groups (3.7 ± 0.3 mcg vs. 3.9 ± 0.3 mcg, $p < 0.80$). The mean dose of morphine received

prior to discharge to home was not significantly different between the two groups (6.6 ± 2.7 mg vs. 8.7 ± 3.1 mg, $p < 0.60$). No significant difference was found between the groups when the amount of ibuprofen taken during the 48-hour period covered by this study (1.9 ± 0.75 Gm vs. 3.2 ± 0.86 Gm, $p < 0.27$). Following analysis with a one-way ANOVA, there was a statistically significant difference between the two groups with regard to amount of postoperative opioid (Roxicet®) usage (7.5 mg ± 9.1 vs. 43.3 mg ± 10.5, $p < 0.02$).

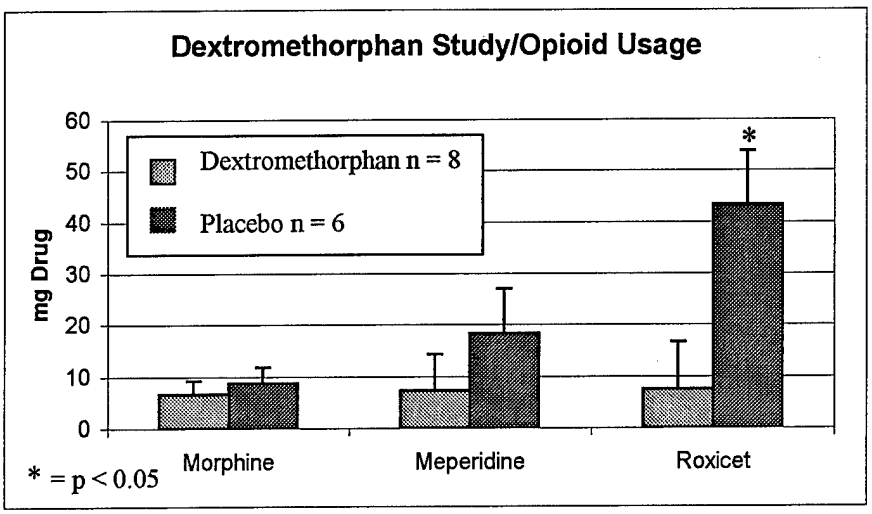

Figure 2. Comparison of postoperative analgesic requirements

Postoperative pain was assessed using a verbal NRS as follows: arrival to the PACU, 15 minutes after arrival, at one hour, at four hours or when discharged home, whichever came first, 6 hours after the end of surgery, 24 hours, and finally at 48 hours following surgery. NRS scores were analyzed by determining the slope of individual subject data points. The slopes of the means for both groups were then compared using one-way ANOVA and Student's t-test. Given the small sample size, comparing the slopes of the means provided a more sensitive test. While there was no difference between groups in the NRS scores during the 48 hours postoperatively (Figure 3), a one-way ANOVA

performed on the slopes of the means for the two groups was significant for the rate of decline in NRS scores ($p < 0.03$) (Figure 4).

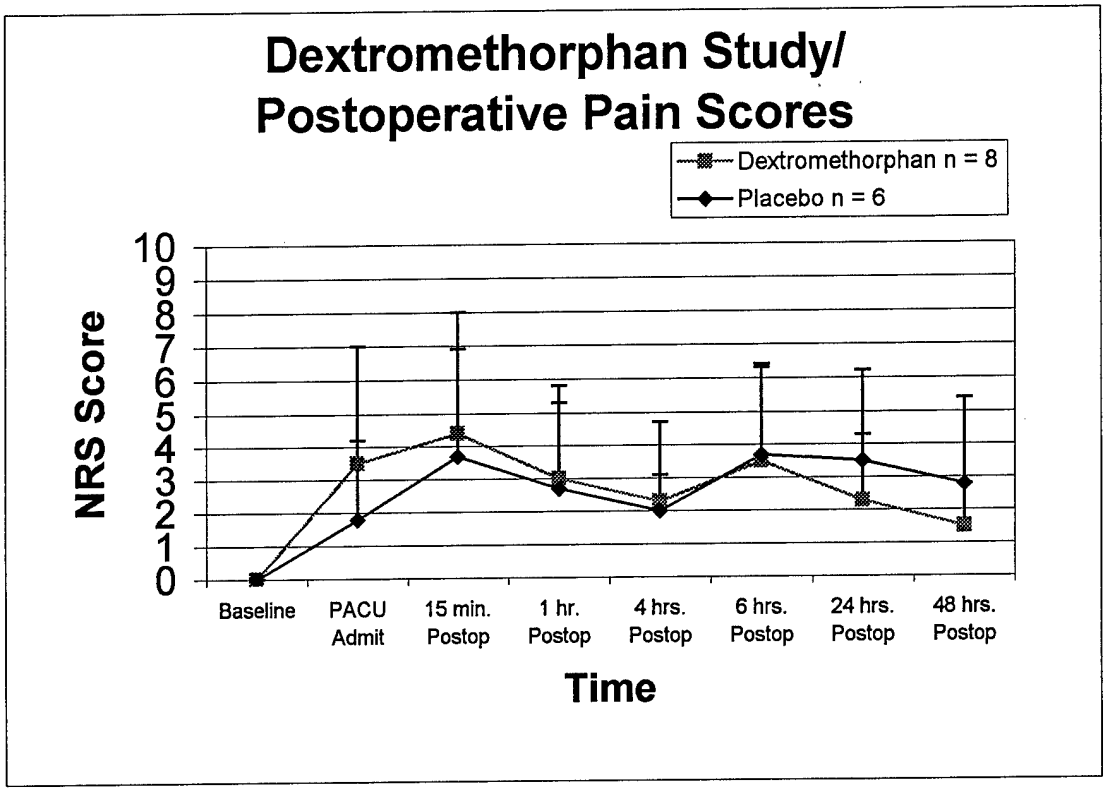

Figure 3. Comparison of postoperative pain scores

Table 4

Slopes of the Means for Subject NRS Scores (N = 14)

	Subjects	Mean of Slopes	Std Error
Dextromethorphan	n = 8	-3.38286 *	1.3371
Placebo	n = 6	1.14333	1.4442

* $p < 0.03$

Data analysis revealed an increase in postoperative pain scores in both groups at 15 minutes and six hours after the end of surgery. In a previous study involving ILBTS patient population, increases in postoperative pain scores were noted at these same time points (Harm & Gibbons, 2000). Several possible factors could account for this increase. During this period, patients were continuing to wake up from their anesthesia and may

have been more aware of their pain. Intraoperatively fentanyl, an opioid of relatively short duration (30 to 60 minutes), was used for analgesia and may have been wearing off. Any postoperative morphine, with an onset time of 15 to 30 minutes following IV administration, they may have received in the recovery room had not yet had time to have an effect.

Both groups had a decrease in mean pain scores at 1 hour and 4 hours postoperatively. During this period, the dextromethorphan group showed a slightly faster decline in pain scores but still remained higher than the placebo group. Six hours postoperatively, both groups showed another increase in mean pain scores, with the dextromethorphan group showing slightly lower mean pain scores for the first time. Possible explanation for the increase seen in both groups might be attributed to: (a) increased activity level requiring use of abdominal muscles, including the car ride home, household activities, and taking care of children all may have contributed to the patient's sensation of pain/discomfort, (b) the analgesia provided by the 0.5% bupivacaine drops had subsided, and (c) discharge pain medication, if taken, had not yet had time to be effective.

Demographic variables including age, ethnicity, ASA category, and body mass index (BMI) were calculated to quantify the sample characteristics using descriptive statistics. There were no statistically significant results found between the two groups. The level of significance determined by convention for this study was set at $p < 0.05$.

As previously mentioned, study participants were asked to complete a take-home questionnaire. Fourteen subjects (100%) completed and returned their questionnaires. The take-home questionnaire asked the study participants to rate their pain six hours after

surgery, 24 and 48 hours after surgery, and to describe the location of their pain and is summarized in table 4.

Table 5

Location of Participants' Pain (N = 14)

Pain location	Group I (n = 8)	Group II (n = 6)
Six hours after surgery		
Abdominal pain	3	2
Abdominal and back pain	2	1
Throat pain	1	0
Incisional pain	2	2
No pain	0	1
Total	8	6
24 Hours Postoperative		
Abdominal pain	3	1
Throat pain	1	0
Abdominal and back pain	1	1
Low back pain	1	0
Incisional pain	2	3
No pain	0	1
Total	8	6
48 Hours Postoperative		
Abdominal pain	1	3
Throat pain	1	0
Abdominal and back pain	0	1

Low back pain	1	0
Incisional pain	0	1
No pain	3	1
Total	8	6

Both groups at six hours after surgery had primarily complaints of abdominal pain (total = 5). One subject in the placebo group reported no pain at any time point following surgery. At 24 hours, incisional pain had replaced abdominal pain as the most frequently reported site of pain. By 48 hours 3 subjects in Group I reported no pain, while only 1 in Group II reported no pain. The take-home questionnaire also provided information on postoperative nausea and vomiting, a common side effect of narcotic use. Doses of dextromethorphan greater than 90 mg are associated with an increase in postoperative nausea. The results of this study were that five of the six patients in the placebo group experienced nausea, and two of these also reported emesis. This, compared to the dextromethorphan group reporting only three of the eight subjects with postoperative nausea, one of these with emesis as well.

Qualitative data collected included asking subjects if they used any other methods to relieve their pain after surgery to include prayer, hot/cold packs, position in bed, meditation, massage, etc. Seven subjects reported they used no other methods to control pain, one used hot packs, four used position in bed, and one used prayer and position in bed to relieve pain.

The following four questions regarding the participants' overall feelings toward surgery/anesthesia services were asked: (a) How was your surgical experience? (b) Was there anything that we could have done differently? (c) How was your overall satisfaction with pain control? (d) What was it like to be in this study?

Thirteen participants were satisfied or very satisfied with their surgical experience, one was dissatisfied with the waiting time. Direct quotations from the participants' answers to the first question, "How was your surgical experience?" include the following:

"I don't remember any of the actual surgery. Everything pre/postop was very professional."

"I did not feel anything. I woke up when they move [sic] me from the bed to the chair."

"My surgical experience was great, except for the pain."

"Good. Staff was very pleasant."

Of the 14 study participants who responded to the question about what could have been done differently, only one expressed consternation with the amount of time in the holding area:

"Minimize wait time; check in 9:30, call back 12:00"

"I'm pleased with everything."

All fourteen subjects reported being satisfied with their postoperative pain control. Direct quotations from the participants' answers to the third question, "How was your overall satisfaction with pain control?" include the following:

"Extremely satisfied only real pain was transitory gas pain. Roxicet relieved pain but I did not sleep for two days."

"Totally satisfied. No complaints."

"Satisfied no extreme pain."

When asked what it was like to be in the study, 12 participants expressed positive aspects ranging from "interesting" to "unaffected, did not interrupt routine." Two subjects did not supply an answer to this question. When asked if they would like a copy

of the study results, 11 subjects wanted a copy, three did not want a copy. Direct quotations from the participants' answers to question four, 'What was it like to be in this study?" include the follow:

"Did not have any affect on my daily plans."

"Nothing to it. Actually felt honored being asked to participate."

"I was glad I could help, if I did at all."

"It is great to be a part of a study that will help others with pain. I think it is great!"

"Interesting."

Summary

There was no significant difference in the total dosage of intravenous rescue medication for postoperative pain received in the hospital. No significant difference was found between the groups when the amount of ibuprofen was compared. Following analysis a statistically significant difference was found in two areas. First, patients who received dextromethorphan 60 mg orally before surgery had a significant decrease in postoperative pain ($p < 0.03$). Secondly, the amount of Roxicet® required postoperatively was statistically less in the dextromethorphan group ($p < 0.02$).

CHAPTER V

Discussion, Conclusions, Implications, and Recommendations

One goal of modern anesthesia is to ensure that patients awaken after surgery with excellent pain control and to maintain pain control throughout the postoperative period (Penning, 1996). As early as 1913, Crile, a surgeon who studied shock and exhaustion following surgery, hypothesized the Principals of pre-emptive analgesia. He proposed that patient outcomes after surgery could be improved by blocking harmful stimuli from reaching the brain (Crile, 1913). This concept of pre-emptive analgesia follows the premise that it is easier to prevent pain rather than titrate medications to reduce pain once it has already been established (Agency for Health Care Policy and Research, 1994). Knowing that several mechanism are responsible for postoperative pain allows us to use different drugs for their specific actions in a multimodal approach to modulate these varying pathways.

Administration of an NMDA receptor antagonist, like dextromethorphan, before surgical trauma, interferes with the intracellular process leading to the hyperalgesic state. Decreased postoperative pain may reduce the untoward physiological and psychological effects associated with pain, possibly improving patient outcomes, and lessening the economical cost of unplanned hospital admissions.

The results from previous studies have varied regarding the effectiveness of dextromethorphan as a pre-emptive treatment to reduce postoperative pain and analgesic consumption. The goal of this study was to compare postoperative pain among ILBTS patients when given 60 mg of dextromethorphan orally versus placebo one hour before

surgery. This chapter begins with a discussion of the research findings, followed by pertinent conclusions, implications for practice, and recommendations for future research.

Discussion

The hypotheses stated that patients undergoing ILBTS who pre-emptively received dextromethorphan 60 mg orally, would experience a difference in (1) the amount of postoperative pain, and (2) the amount of opioid administered postoperatively. This study was designed in such a manner as to minimize possible extraneous variables, and included the following: (a) standardizing the anesthetic which included, (b) no oral gastric tube in order to not remove any remaining oral drug, (c) allowing time for the pre-emptive medication to be absorbed prior to incision, (d) initiating a standardized postoperative analgesic prescription, and (e) having the surgeons standardize their method of fallopian tube occlusion. This design may help explain why these findings were so clearly measured in such a small sample as represented in this pilot study.

Initially NRS scores for the dextromethorphan group were higher than the placebo group; however from six to 48 hours postoperatively, NRS scores for the dextromethorphan group were lower. While the difference in NRS score was not statistically significant the placebo group required nearly six times as much narcotic to achieve pain relief that did not approach the same level of relief experienced by the dextromethorphan group. Further, the rate of decline in NRS scores following surgery was significantly different in the dextromethorphan group ($p < 0.03$). This increased rate of decline in NRS for the dextromethorphan group may have achieved significance if scores had been collected for a period greater than 48-hours. This may have implications

for surgical procedures associated with postoperative pain that last longer than that associated with ILBTS.

Despite the small sample size, this pilot study clearly showed a significant difference in the amount of postoperative narcotic analgesics used by women following ILBTS. Side effects associated with the use of narcotics include nausea, vomiting, respiratory depression, somnolence, and constipation. With the exception of nausea and vomiting, information on incidence of these side effects was not collected. The decreased incidence of nausea and vomiting found in this study, 83% for placebo versus 37% for dextromethorphan, supports the use of pre-emptive dextromethorphan to decrease the incidence of postoperative nausea associated with narcotic use. The dose of dextromethorphan used for this pilot study appears to have good analgesic sparing effects, and decreasing postoperative nausea, while avoiding the adverse effect associated with larger doses.

Four types of pain after laparoscopic sterilization have been reported. Subphrenic/ shoulder pain is the first type of pain, and may persist until the third to fourth postoperative day (Alexander, 1997; Dobbs et al., 1987; Goldstein et al., 2000; Guard & Wiltshire, 1996). None of the patients in this study reported this type of pain. This may have been due to adequate removal of the carbon monoxide at the end of surgery. This would be consistent with previous studies that have shown removal of insufflation gas at the end of procedure to greatly reduce this type of pain. Deep pelvic pain is the second type of pain, and rarely lasts for more than six hours postoperatively (Alexander, 1997; Chi & Cole, 1979; Davis & Miller, 1988; Dobbs et al., 1987; Goldstein et al., 2000; Pelland, 1987). None of the patients in this study reported deep pelvic or

spasmodic/cramping pain. However, the incidence of reported abdominal pain probably encompasses these two types of pain. In the literature this pain has been reported to last no more than six hours, and can often be prevented or at least decreased by the topical administration of 0.5% bupivacaine, as was done in this study (Ezeh et al., 1995; Goldstein et al., 2000; Wheatley, Millar, & Jadad, 1994). By the time the bupivacaine had worn off, this pelvic pain would have largely subsided. One other explanation may be that patients did not differentiate between pelvic pain and abdominal pain in general. Spasmodic/cramping pain is the third type of pain, and hardly ever lasts longer than three to four hours (Dobbs et al., 1987; Edwards et al., 1991; Guard & Wiltshire, 1996). The take-home questionnaire revealed that eight subjects (six hours after surgery), four subjects (24 hours), and five subjects (48 hours) reported abdominal pain.

Incisional pain is the fourth type of pain. Four participants responded on the home questionnaire with complaints of incisional pain six hours after surgery, five had this type of pain at 24 hours, and only one patient in the placebo group reported this type of pain at 48 hours. The trocar insertion sites are small incisions, approximately one inch in length each. The fact this was the most persistent type of pain reported indicates that dextromethorphan is probably less effective at decreasing incisional pain compared to the other types of pain.

During data analysis several incidental findings were noted. One such finding was that one patient had been discharged to home with an NRS score of five. This was contrary to the protocol already established in the same day surgery clinic. However, there was no documentation as to whether this level of reported pain was either manageable or tolerable by the patient. During the forty-eight hour postoperative period

this individual's NRS score was never lower than four. There may be several plausible explanations. One may be related to the patient's understanding of the discharge protocol. That is, she may have requested to be released and subsequently reported that a rating of "5" was in fact manageable in order to be discharged home. Perhaps she wanted to leave as soon as possible in an effort to complete her convalescence at home. Moreover, her perception of the pain postoperatively may have been less than her expectation.

Three patients reported a different NRS score for the 6 hours postoperative, 24 hour and 48 hour scores during the follow-up telephone two days after surgery. The NRS score reflected on the take-home questionnaire was always higher than what was reported during the telephone follow-up interview. Possible explanations include that the patient was relying on memory of the scores when reporting them telephonically. Another possibility is that when questioned, subjects may have felt compelled to respond in order to please the investigators (known as demand characteristics), as noted by Orne (1962). Because all take-home questionnaires were returned, the NRS score was used for purposes of data analysis and not the scores reported telephonically.

Interestingly, some of the OB/GYN surgeons continued to request 0.5% bupivacaine local anesthetic for application on the tubes for all their patients undergoing ILBTS. This change in practice was due in part to their having noticed a decrease in postoperative pain during the immediate postoperative period. Several had also requested literature on the use of local anesthetic for post-laparoscopic tubal operations. Also some of the senior residents had previous experience with use of local anesthetic for tubal ligation patients from a previous study performed at the site where this research was performed.

Theoretical Framework Used to Guide Research

The theoretical framework for this study used a physiological model depicting central and peripheral mechanisms that have been studied in the pain pathway. Based on current knowledge about the various mechanisms responsible for postoperative pain, it seems reasonable that a multimodal approach to pre-emptive analgesia would be more effective. Following a multimodal approach to pre-emptive analgesia has been supported by the studies of Dahl & Kehlet (1993), Goodwin (1998), Kissin (1996), and Woolf & Chong (1993).

In addition, a pharmacological model provided a viable approach to pre-emptively mediate pain that is transmitted via the aforementioned pathways by inhibition of the NMDA receptor. As previously discussed, dextromethorphan's noncompetitive inhibition of this receptor in the central nervous system halts the production of prostaglandins via cyclooxygenase synthase, nitric oxide via nitric oxide synthase and the potentiation of the NMDA receptor by the phosphorylating actions of phosphokinase C. These mechanisms all lead to the hyperalgesic state referred to as "wind-up". Another goal of the study design was for the dextromethorphan to approach peak serum levels by the time direct laryngoscopy was performed. The Principal Investigator believes this was achieved; the dextromethorphan group had a mean of 61.5 minutes from the time of administration until laryngoscopy.

Prior to this study, several of the OB/GYN surgeons at the institution where this study was performed included the use of 0.5% bupivacaine drops applied to the tubes of the patients in both groups. The review of literature supported the analgesic effectiveness of this technique in the immediate postoperative period and I elected to standardize its

use in this study as part the multimodal approach to postoperative pain (Ezeh et al., 1995; Goldstein et al., 2000; Wheatley et al., 1994).

Information on location of pain was collected, but no descriptive information on quality of pain was collected. This information may have helped to distinguish between incisional pain, versus visceral, versus the pain associated with carbon dioxide insufflation. Qualitative data was collected on the take-home questionnaire; analysis provided supplemental information that added depth to the quantitative findings. Also, some of the comments, gleaned from the participants, impact clinical practice. Finally, analysis of the take-home questionnaire data stimulates many questions that warrant future research.

Conclusions

The findings from this study suggested that the pre-emptive administration of dextromethorphan may be an effective means of mitigating postoperative pain in women undergoing ILBTS.

Clinical Implications

In the facility where the study was conducted, the unit dose cost for 60 mg dextromethorphan was $4.23. Pre-emptively medicating this surgical population with 60 mg dextromethorphan orally might provide a decrease in treatment cost as represented by a decrease need for postoperative analgesics. Also decreased postoperative pain and side effects associated with narcotics may lead to increased patient satisfaction. The results of this study supported the use of dextromethorphan women undergoing ILBTS . Based on this study and the work of other researchers the administration of 60 mg of

dextromethorphan orally at least one hour prior to planned time of direct laryngoscopy to allow for adequate onset and peak effect.

Pain score results show that if a patient had a hypothetical NRS score of "5", 15 minutes after the end of surgery, the patient could expect to have a similar level of postoperative pain at 6 hours following the end of surgery. This could be useful in the form of discharge teaching; if pain is perceived as unmanageable or uncomfortable by the patient at 15 minutes, then discharge teaching could include taking medications regularly up through bedtime to preempt postoperative pain that will predictably result.

Of final importance to note is the following, there were several comments on the take-home questionnaire that addressed concerns about delays in proceeding to the operating room. Suggestions from the women included informing patients about possible delays preoperatively, and then keeping them updated when delays occur. Reminding staff to keep patients informed has immediate clinical implications that can significantly affect perceptions of the surgical experience.

Recommendations for Future Research

Postoperative pain control in this surgical population continues to present as an anesthetic challenge. Anesthesia providers are continually seeking both pharmacologic and non-pharmacologic modalities that are both cost-effective and clinically effective. This new use for an old drug may provide one more option in the nurse anesthetists' armamentarium to decrease postoperative pain, and potentially improve patient outcomes. While not normally stocked in a hospitals pharmacy as pure dextromethorphan, it can be ordered from manufacturers in the United States. An intravenous form is available in some Asian and European countries, but has not yet been

approved for use in this country. The availability of an intravenous form would be especially convenient in the preoperative period with its ease of administration and bypassing the alimentary tract resulting in a quicker onset of action. As more data is collected on the analgesic sparing effects of dextromethorphan, interest in obtaining approval for intravenous dextromethorphan in the United States may increase. However, even with only an oral form currently available the results of this study lend support for the pre-emptive use of dextromethorphan in women having ILBTS. Since this was a pilot study, further studies with a larger sample are warranted. The usefulness of oral dextromethorphan needs to be explored in other patient populations.

While the take-home questionnaire inquired as to where the subject's pain was located, it did not have them provide details regarding the quality of their pain. A future descriptive study could be designed to discern whether subjects are experiencing incisional pain, or actually having deep pelvic or spasmodic type of pain.

This study was conducted in a military treatment facility (and teaching hospital) where the study participants were either active duty service members or dependents of active duty service members. Generalizations are only applicable to similar populations. Therefore, a repeat of this study in a non-military/non-teaching facility should be conducted to explore if there is a similar strong finding. Again, the pre-emptive use of dextromethorphan in other patient populations warrants study in non-military, non-teaching facilities. This study measured quantity of pain experienced but not the quality, which could be a rich area for research.

Summary

This prospective, double-blind, randomized pilot study examined the effects on postoperative pain when ASA I or II female patients presenting for laparoscopic tubal sterilization were given either 60 mg dextromethorphan orally or placebo. Group I (received dextromethorphan) consisted of 8 participants while Group II (placebo) had six subjects. Overall, pain scores in the dextromethorphan group were consistently lower compared to the placebo group but failed to reach statistical significance. However, when the rate of decline in pain scores was analyzed by comparing the means of the slopes, there was a significant difference in the rate of decline ($p < 0.04$).

Analgesic consumption during the forty-eight hours following surgery was significantly lower in the dextromethorphan group compared to placebo ($p < 0.02$). While no significant difference in NRS scores was detected for individual data collection points, the placebo group required eight times as much postoperative narcotic and still reported NRS scores that were higher from six through forty-eight hours postoperative.

Based on the results obtained in this pilot study, the decision was made to proceed with a full study comprised of twenty-five subjects in each group. It is now being conducted at the facility where this pilot study was performed.

APPENDIX A

Conceptual Framework

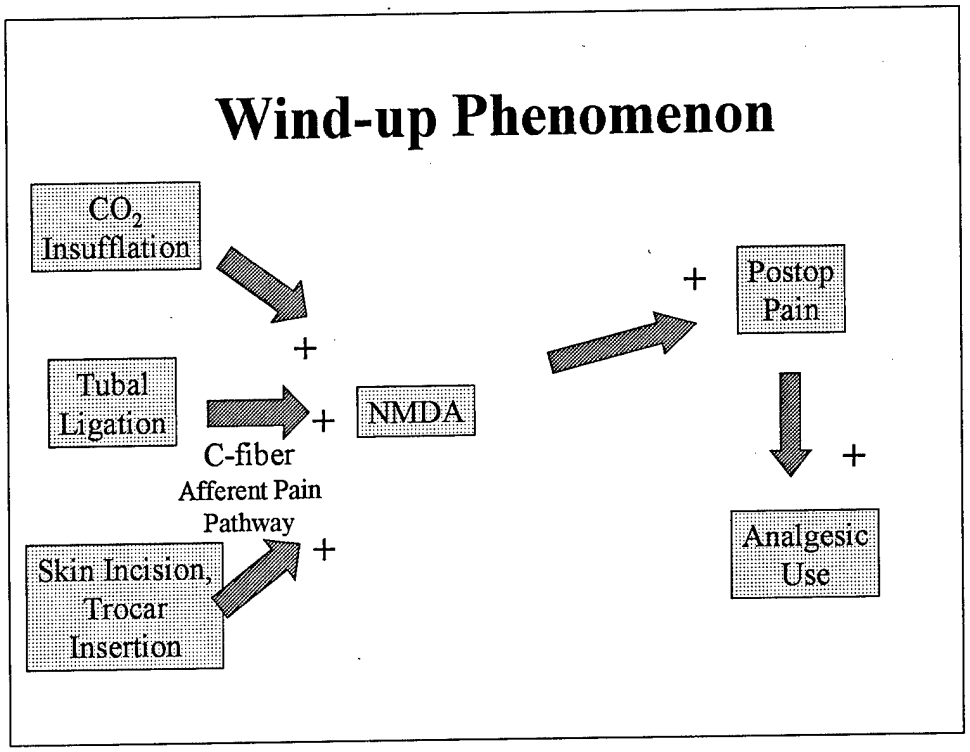

Figure 4. Wind-up model of pain: Influence of NMDA pathway on postoperative pain.

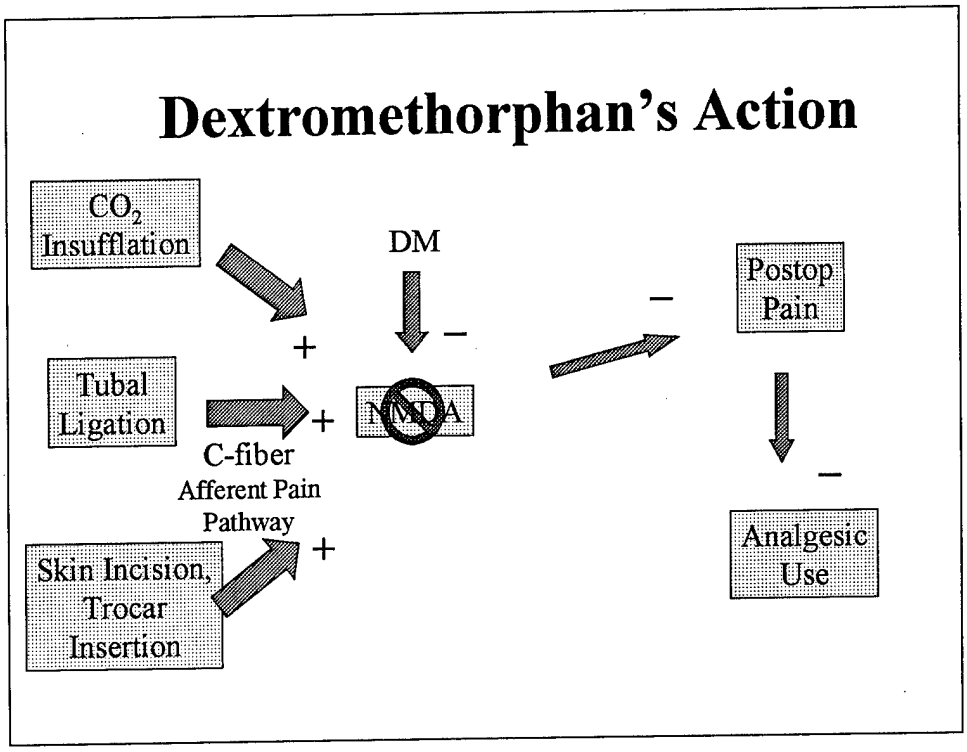

Figure 5. Model of dextromethorphan's action: Influence of dextromethorphan on interrupting the NMDA receptors role in the wind-up phenomenon.

APPENDIX B

Exclusion Criteria Worksheet

Exclusion Criteria Worksheet for Tubal Sterilization Study

Instruction, please answer the questions below, if any are marked, the patient is **not** eligible for my study. Mahalo for helping with my study.

Please put a checkmark if the patient has any of the following **exclusion** criteria:

_____ Does not understand English.

_____ Less than 18 years old.

_____ Weighs less than 110 pounds.

_____ Currently using MAO inhibitors.

_____ Is allergic to Dextromethorphan.

_____ Has liver problems.

_____ Has kidney problems.

_____ Less than six weeks postpartum on day of surgery.

APPENDIX C

Data Collection Worksheet

Data Collection Worksheet

Preoperative Data

Patient ID # _____ Date of Surgery_____

Demographic/Preoperative Data

Age: _____ Height: _____ (cm) Weight: _____ (kg) BMI: _____ LMP: _____

ASA: _____ Ethnicity: _____

Numeric rating Scale: (to include location of pain)

Preoperative: _____ Location: _____ Time: _____

Time given DM/Placebo: _____

Intraoperative Data

Time of laryngoscopy: _____ Estimated time since DM/Placebo: _____ (min)

Time of first incision: _____

Time when first fallopian tube occluded: _____ Type of tube occlusion: _____

Duration of Surgery: _____ (min)

Local anesthetic used?: Yes No Type: _____ Amount: _____(mg)

Anesthetic/Meds, protocol met? Yes No

Postoperative Data

PACU arrival time: _____ Discharge time: _____

Time of first administration of postoperative medication: _____

Nausea: YES NO Time: _____

Emesis: YES NO Time: _____

Antiemetics received: Type: _____ Amount: _____ Time: _____

Total dose & type of postoperative analgesic adminstration _____

Admitted?: YES NO If yes, why? _____

Verbal Analog Scale scores and location of reported pain

Time	**Pain Score**
_____ Immediately on arrival to PACU	_____ Location _____
_____ 15 min. after arrival PACU	_____ Location _____
_____ 1 hour postop, or discharge from PACU	_____ Location _____
_____ 4 hours postop, or discharge from SAC	_____ Location _____
_____ 6 hours postop	_____ Location _____
_____ 24 hours postop	_____ Location _____
_____ 48 hours postop	_____ Location _____

Time of discharge from hospital: _____

Take-home questionnaire returned? YES NO

Return phone call comments:

_____

_____

_____

_____

_____

APPENDIX D

Volunteer Agreement Affidavit

VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25 or AR 40-38, the proponent agency is OTSG

PRIVACY ACT OF 1974

Authority: 10 USC 3013, 44 USC 3101, and 10 USC 1071-1087

Principle Purpose: To document voluntary participation in the Clinical Investigation and Research Program, SSN and home address will be used for identification and locating purposes.

Routine Uses: The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study. Implementation of medical programs, adjudication of claims, and for the mandatory reporting of medical conditions as required by law. Information may be furnished to Federal, State and local agencies.

Disclosure: The furnishing of your SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A(1) - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____ SSN_____.

having full capacity to consent and having attained my _____birthday, do hereby volunteer/give

consent as legalrepresentative for _____ to

participate in _____

The Effect of Preemptive Administration of Dextromethorphan on Postoperative Pain in Patients Undergoing Interval Laparoscopic Bilateral Tubal Sterilization.

under the direction of CPT Brian M. Pitcher, AN

conducted at Tripler Army Medical Center, Tripler AMC, HI 96859-5000

The implications of my voluntary participation/consent as legal representative; duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by_____
I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights/the rights of the person I represent on study-related injury, I may contact
the Center Judge Advocate

at Tripler Army Medical Center, Tripler AMC, HI 96859-5000 (808) 433-5311

I understand that I may at any time during the course of this study revoke my consent and withdraw/have the person I represent withdrawn from the study without further penalty or loss of benefits; however, I/the person I represent may be required (military volunteer) or requested (civilian volunteer) to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary for my/the person I represent's health and well-being. My/the person I represent's refusal to participate will involve no penalty or loss of benefits to which I am/the person I represent is otherwise entitled.

APPROVED BY TAMC IRB
JAN 18 2001

PART A (2) - ASSENT VOLUNTEER AFFIDAVIT *(MINOR CHILD)*

I, _____, SSN _____ having full

capacity to assent and having attained my _____ birthday, do hereby volunteer for _____

_____ to participate in _____

_____
(Research Study)

under the direction of _____

conducted at _____
(Name of Institution)

PART A (2) - ASSENT VOLUNTEER AFFIDAVIT *(MINOR CHILD) (Cont'd.)*

The implications of my voluntary participation; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights I may contact

at _____
(Name, Address, and Phone Number of Hospital (Include Area Code))

I understand that I may at any time during the course of this study revoke my assent and withdraw from the study without further penalty or loss of benefits; however, I may be requested to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

PART B - TO BE COMPLETED BY INVESTIGATOR

PARTICIPATION INFORMATION: You have been invited to participate in a clinical research study conducted at Tripler Army Medical Center. It is very important that you read and understand the following general principles. (1) Your participation is entirely voluntary. (2) You may withdraw from participation in this study or any part of the study at any time. (3) Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. After you read the explanation, please feel free to ask any questions that will allow you to clearly understand the nature of the study.

NATURE OF STUDY: You have been invited to participate in this study because you are having a bilateral tubal sterilization. The purpose of the study is to determine if taking oral dextromethorphan (common ingredient in cough syrup) before your operation makes a difference in the amount of pain you experience after your operation. We will be comparing two groups, one will receive the study medication mixed in a sweet tasting liquid, and the other will receive only the sweet liquid with no medication added to it, also known as a placebo (a placebo is like a sugar pill, and has no medical effect). Both groups will receive the same standard pain medications for this procedure as well as take home pain medications. During this study, you will receive either the study drug or placebo before your operation. Several published studies have indicated that dextromethorphan reduces pain following similar surgical procedures.

EXPECTED DURATION OF SUBJECT'S PARTICIPATION: Your participation in this study will begin when you arrive in the Surgical Admission Center the day of your operation. Your participation in this study will end when you are contacted by phone two days after your operation, and after you return the home questionnaire. Therefore, your participation in the study will be for about six to eight hours while in the hospital. Additionally, you will receive a follow-up phone call at your home two days after your operation, and you will need to fill out a short questionnaire. The call will take about five to ten minutes of your time, and the questionnaire will take an additional five to ten minutes of your time.

Patient's Initials _____ Witness' Initials _____

Volunteer Agreement Affidavit

WHAT WILL BE DONE: After agreeing to participate in this study, you will be randomly assigned into a group that receives either dextromethorphan or the placebo. Random assignment is a process like flipping a coin, and means that you have about an equal chance of being assigned to either group. The drug and placebo will be coded, so that neither you nor the individual providing your anesthesia will know which of the two groups you are in, or whether you are receiving dextromethorphan or placebo. Should your medical condition require it, we can break the study drug code to determine which drug you are receiving and provide any other treatment that is necessary.

When you arrive at the Surgical Admission Center, you will be given a sweet liquid to drink (one hour before your operation). The liquid will either contain 60 milligrams total of dextromethorphan, or just the sweet liquid. Before your operation, we will ask you to rate your pain on a scale of zero to ten, with zero being no pain and 10 being the worst pain possible. We will also ask you to describe the location of your pain. We will ask you to rate any pain you may be having, and its location, seven more times after this: (1) when you first get to the recovery room after your operation, (2) 15 minutes after you get to the recovery room, (3) one hour after your operation, (4) four hours after your operation or when you are discharged from the recovery room, whichever comes first, (5) six hours after your operation, (6) 24 hours after your operation, and (7) at 48 hours following your operation.

You may request additional pain medication at any time during this study. Your participation in the study will not affect your ability to receive additional pain medications.

We will give you a short questionnaire to take home, to rate your pain and its location (six hours after your operation and at 24 and 48 hours after your operation). This questionnaire includes the same pain rating scale that you will use while here in the hospital, it also asks about the location of your pain. We will call you at home two days after your surgery, to ask how you are doing, and to ask about your last three pain rating scores. We will also give you a stamped, addressed envelope so you can return the questionnaire to us.

REASONABLY FORESEEABLE RISKS OR DISCOMFORTS: The risks and benefits of bilateral tubal sterilization and anesthesia have been explained to you separately, and you have signed a separate consent for the operation. Dextromethorphan is found in many brands of cough syrup and has a long safety history and no significant side effects at the dose you may receive. Allergic reactions can occur with any medication. An allergic reaction may create generalized swelling and sudden changes in heart rate and blood pressure. Dextromethorphan should not be given to patients taking a specific type of antidepressant called monoamine oxidase inhibitors (MAOI).

Patient's Initials _____ Witness' Initials _____

Volunteer Agreement Affidavit

Before you were invited to participate in this study, we screened you carefully to ensure that you have no health problems that might make it more likely for you to have any of these side effects. Additionally, these side effects are very rare when you are receiving only one dose of these medications. Also, we will be calling you at home two days after your surgery, and you may perceive this as a minor inconvenience.

COMPENSATION FOR INJURY: In the event of physical injury or illness resulting from the research procedure(s), medical treatment is available and compensation may be available. For information regarding legal aspects of participation, contact the Center Judge Advocate, at (808) 433-5311.

BENEFIT(S) TO THE SUBJECT OR TO OTHERS: There may be no benefit to you from participating in this study. One of the goals of anesthesia is to control pain, to include pain control during initial recovery from the operation. If receiving dextromethorphan in this study provides better pain relief than the placebo, you may have less pain following your operation. Good pain control should improve your satisfaction with your operation and the outcome of your operation. Additionally, choosing the best method of controlling pain, may reduce the potential for complications from the medications or operation. This could mean that patients in the future might have less pain, have fewer complications, and be less likely to be readmitted to the hospital. You will not be paid for participating in this study.

ALTERNATIVE PROCEDURES OR COURSES OF TREATMENT: You may choose not to participate in this study. If you choose not to participate, your anesthesia care (including pain medication) will be the standard of care for your procedure.

CONFIDENTIALITY: Information gained because of your participation in this study may be publicized in the medical literature, discussed as an educational model, and used generally in the furtherance of medical science. Information from this study may be used as part of a scientific publication in medical or professional journals, but you will in no way be personally identified. Complete confidentiality cannot be promised to active-duty military personnel because information bearing on your health may be reported to appropriate medical or command authorities.

PRECAUTIONS TO BE OBSERVED BY SUBJECT BEFORE AND FOLLOWING THE STUDY: There are no precautions to follow that are specific to your participation in this study.

CIRCUMSTANCES UNDER WHICH YOUR PARTICIPATION MAY BE TERMINATED WITHOUT YOUR CONSENT: (a) Health conditions or other conditions that might occur which may be dangerous or detrimental to you or your health; (b) if military contingency requires it; (c) if you become ineligible for military care as authorized by Army regulation; (d) if the safety monitor determines that continued treatment under this study may be harmful to you.

Patient's Initials _____ Witness' Initials _____

Volunteer Agreement Affidavit

ADDITIONAL COSTS TO SUBJECT THAT MAY RESULT FROM PARTICIPATION IN STUDY: In accordance with AR 40-38, paragraph 3-3(j)(2), daily charges for inpatient care will be waived while the volunteer is in the hospital if the volunteer would not normally enter the hospital for treatment but is requested to do so as part of a research study or as a result of adverse reaction to the drug(s) or procedure(s) used in this study. This also applies to the volunteer's extension of time in a hospital for a research study when the volunteer is already in the hospital.

SIGNIFICANT NEW FINDINGS: Any significant new findings developed during the course of this study which could affect your willingness to continue participation will be made available to you. The results of the research will be made available to you if you so desire. Complete results may not be known for several years.

APPROXIMATE NUMBER OF SUBJECTS INVOLVED IN THE STUDY: Approximately 50 patients.

DOMICILIARY CARE STATEMENT: The extent of medical care provided, should it become necessary, is limited and will be within the scope authorized for Department of Defense (DOD) health care beneficiaries. Necessary medical care does not include domiciliary (home or nursing home) care.

FOR FURTHER INFORMATION: Please contact the principal investigator,

CPT Brian M. Pitcher, Student Registered Nurse Anesthetist
Department of Nursing/Department of Health Education and Training
(808) 433-2132

IF THERE IS ANY PORTION OF THIS EXPLANATION THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING. A COPY OF THE VOLUNTEER AGREEMENT AFFIDAVIT WILL BE PROVIDED TO YOU.

I have read the above explanation and agree to participate in the investigational study described.

Printed Name & Signature of Volunteer _____ Date _____

Printed Name & Signature of Witness _____ Date _____

Patient's Initials _____ Witness' Initials _____

APPENDIX E

Home Questionnaire

Home Questionnaire

Aloha and Mahalo for agreeing to participate in my study. I wish you a speedy recovery and will be calling you two days after your surgery to see how you are doing after surgery. Please take time to fill out this questionnaire prior to my calling you. Whether I am able to contact you or not, please mail this completed form back to me within 2-3 days with the self-addressed and stamped envelope provided. Thank you again for participating in my study!

Using the table below please record the amount of pain you were having at the indicated times using the same pain scale you used in the hospital. 0 being no pain and 10 being the worst pain you can imagine. Also please enter the type and number of pain medications you took for that time period.

Date/Time	Amount of Pain	Where Is Your Pain Felt
Date: Time:	Score:	
Date: Time:	Score:	
Date: Time:	Score:	

Please Record the date and times for any pain medications on the reverse of this form

Date and Time	Medication Name	Number of Pills Taken

In addition to the above, please take the time to answer the following questions.

1. Are there any other methods that you used to relieve your pain after surgery (prayer, hot/cold packs, position in bed, meditation, etc.)? _____

_____

_____.

2. Did you have any nausea after leaving the hospital? YES NO

3. Did you vomit after leaving the hospital? YES NO

Please answer the following questions regarding your surgery/anesthesia service:

1. How was your surgical experience?

2. Is there anything we could have done differently?

3. How was your overall satisfaction with pain control?

4. What was it like to be in this study?

5. Which group did you think you were in for this study (drug or placebo)?

6. Would you like a copy of the results? YES NO

If yes please provide you address (Results will be available around Nov. 2001)

Mahalo!

APPENDIX F

TAMC Human Use Committee Approval Letter

MCHK-CI (40-38a)

JAN 1 8 2001

MEMORANDUM FOR CPT Brian M. Pitcher, AN, Department of Health Education & Training, (ATTN: MCHK-HE), Tripler AMC, HI

SUBJECT: Approval to Initiate More Than Minimal Risk Study

1. Your clinical investigation project entitled "TAMC 11H01: The Effect of Preemptive Administration of Dextromethorphan on Postoperative Pain in Patients Undergoing Interval Laparoscopic Bilateral Tubal Sterilization" completed required review by the Institutional Review Board (IRB) on 20 November 2000 and is approved to start immediately.

2. **Please note that this is NOT an approval to receive extramural resources** (ie, personnel, drugs, supplies, equipment, money, and gifts from any source outside of TAMC) **nor an indication of guaranteed funding from the Department of Clinical Investigation.** If any extramural resources are received without DA or MEDCOM approval, the individual who receives them may be found in ethics violation and prosecuted for criminal misconduct. You must coordinate extramural resource approvals with the Department of Clinical Investigation, Bldg 40, 433-6709.

3. Your study has more than minimal risk, and the medical monitor assigned is LTC Kenneth C. Harris, MC. (S)He has the authority to require changes to your study or even suspension of your research to protect the safety of the volunteers. It is your responsibility to keep the medical monitor continuously informed of the status of your work and in particular to immediately report any sign or symptom suggesting adverse effect or increased risk of a volunteer, whether or not that increased risk is thought to be due to the research. The medical monitor's recommendations and requests are to be complied without failure or delay; if you cannot comply, suspend all research on this protocol immediately and notify me directly. Once a safety measure is instituted, it may not be dropped without review of the Human Use Committee and command decision.

4. Should any of the volunteers experience signs or symptoms of adverse effects or illness, you must insure immediate medical referral to the appropriate Tripler AMC health care team. You must document all such occurrences, whether or not caused by your research, and report them to the Human Use Committee. Your medical monitor will advise you whether or not that report can wait for your annual review.

5. You must report your study findings, including number of patients and adverse effects, to the Human Use Committee prior to one year from this date (or earlier if required to do so by the medical monitor). You must also report your study in the TAMC Annual Report of Clinical Investigation Activities. You will be given full instructions, including schedule of reports, from the Chief, Clinical Investigation, 30 days prior to any report suspense.

MCHK-CI
SUBJECT: Approval to Initiate More Than Minimal Risk Study

6. Your study and its documentation, including list of volunteers and copies of the volunteers' informed consent statements, are subject to inspection at any time by your chain of command and by such inspectors of official audit agencies as obtain prior consent from this command. You must maintain your records such as to facilitate such inspections.

7. Any public presentations or publications of your work must receive prior clearance of this command. This includes academic lectures given outside TAMC, abstracts submitted to professional meetings, letters to the editor and press releases.

8. Your research study has been determined to be of potential importance to the academic and professional program of Tripler AMC. You are to give all possible priority to its completion. Should any problem arise that jeopardizes the success of your research, notify the Chief, Clinical Investigation, at 433-6709.

Encl

for RICHARD R. JEFFRIES
CAPT, MC, USN
Deputy Commander for Clinical Services
Chair, Human Use Committee

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Vita

Brian M. Pitcher was born on November 27, 1961 to Robert and Sandra Pitcher in Connersville, Indiana. After graduating from Bloomington South High School in 1980, he attended Indiana University in Bloomington Indiana, graduating with a Bachelor of Science degree in Microbiology in 1985. Following graduation, he accepted a position at Indiana University as a research assistant in the Biology Department while awaiting appointment into the U. S. Air Force. He was commissioned into the U. S. Air Force in 1986 to attend Navigator Flight Training School and later Electronic Warfare School. From 1988 to 1991 he was an Electronic Warfare Instructor for B52 G/H with the 60th Bomb Squadron, Anderson AFB, Guam and later the 325th Bomb Squadron, Fairchild AFB, Spokane, Washington. In 1991 he left the Air Force to pursue a Bachelor of Science degree in Nursing. He attended and graduated Cum Laude from Washington State University, Pullman, Washington in 1994. After graduation he reentered the Air Force as a registered nurse, working in the Surgical Intensive Care Unit, Wilford Hall Medical Center, Lackland AFB, San Antonio, Texas. In 1999 he applied to and was accepted into the U. S. Army Graduate Program in Anesthesia Nursing where he is currently enrolled.